EXHIBIT 1

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Criere et al.

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(54) **PHARMACEUTICAL COMPOSITION CONTAINING FENOFIBRATE AND THE PREPARATION METHOD**

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A61K 9/56 (2006.01)
A61K 9/58 (2006.01)

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(58) **Field of Classification Search** 424/489, 424/462, 456, 459, 497, 490; 514/49
See application file for complete search history.

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(57) **ABSTRACT**

The invention concerns a pharmaceutical composition containing micronized fenofibrate, a surfactant and a binding cellulose derivative, as solubilizing adjuvant, preferably hydroxypropylmethylcellulose. The cellulose derivative represents less than 20 wt. % of the composition. The association of micronized fenofibrate with a binding cellulose derivative, as solubilizing adjuvant and a surfactant enables enhanced bioavailability of the active principle. The invention also concerns a method for preparing said composition without using any organic solvent.

34 Claims, 4 Drawing Sheets

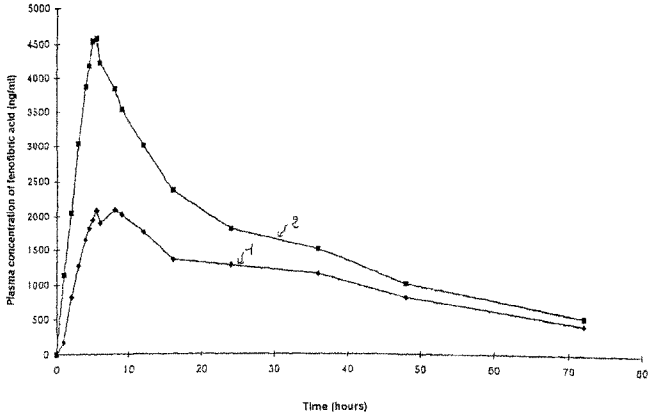

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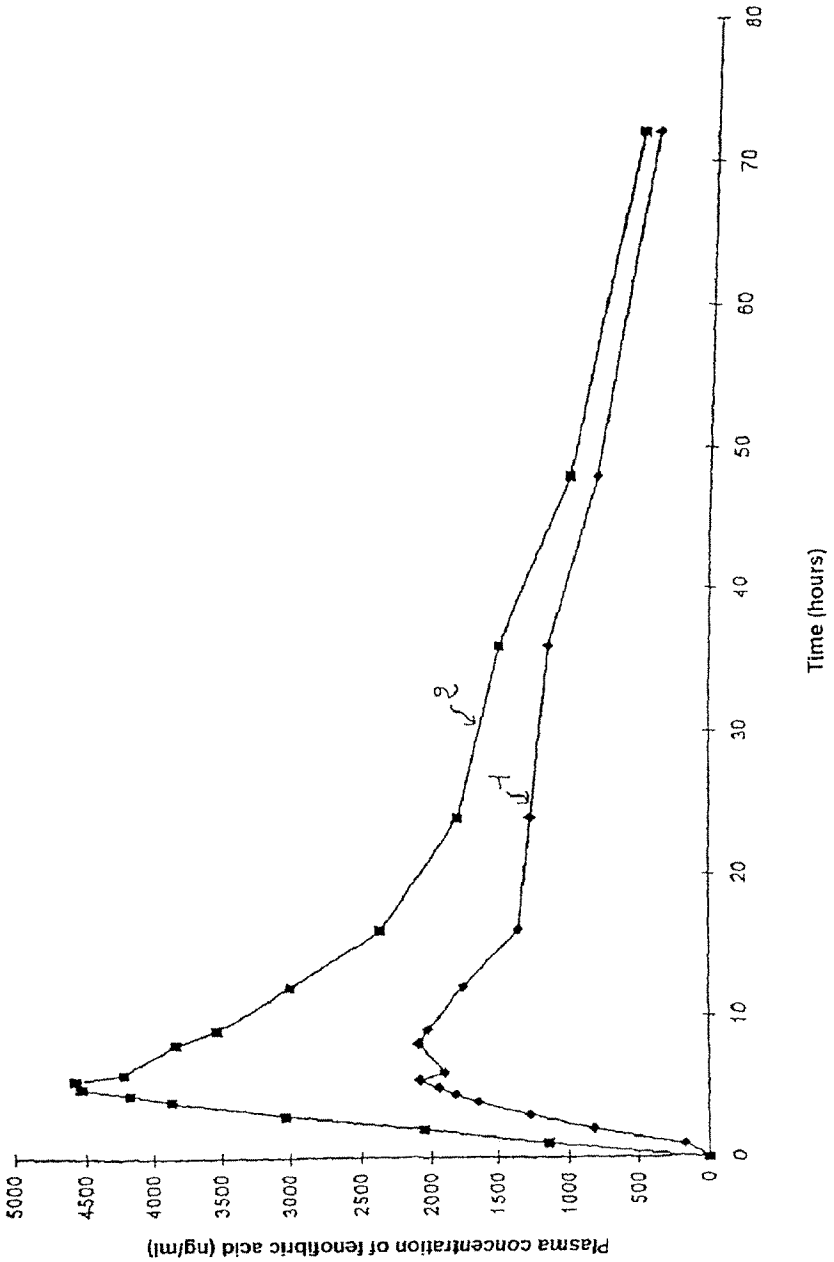
Figure 1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4500
4000
3500
3000
2500
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1500
1000
500
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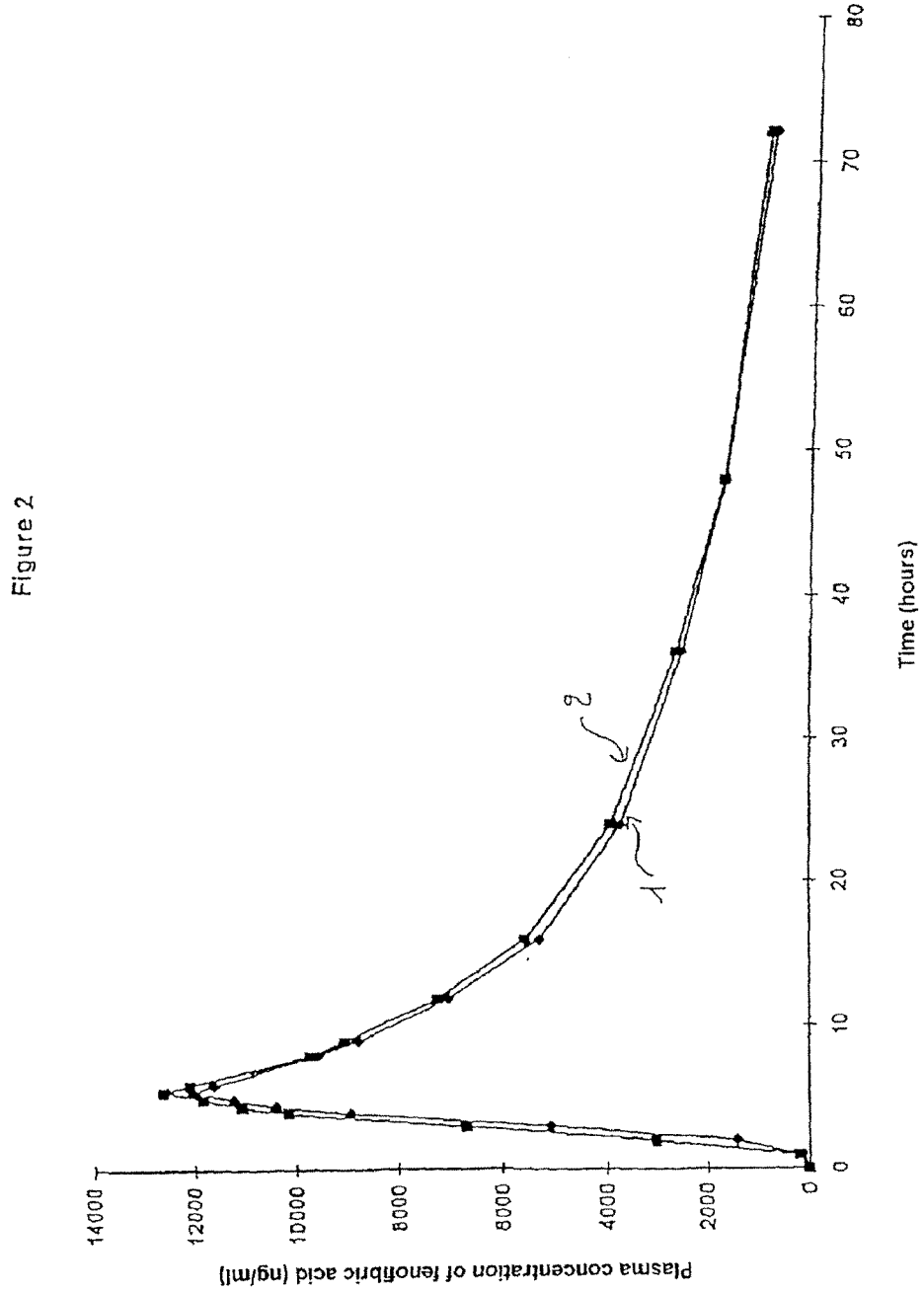
10
20
30
40
50
60
70
80
Time (hours)
2
1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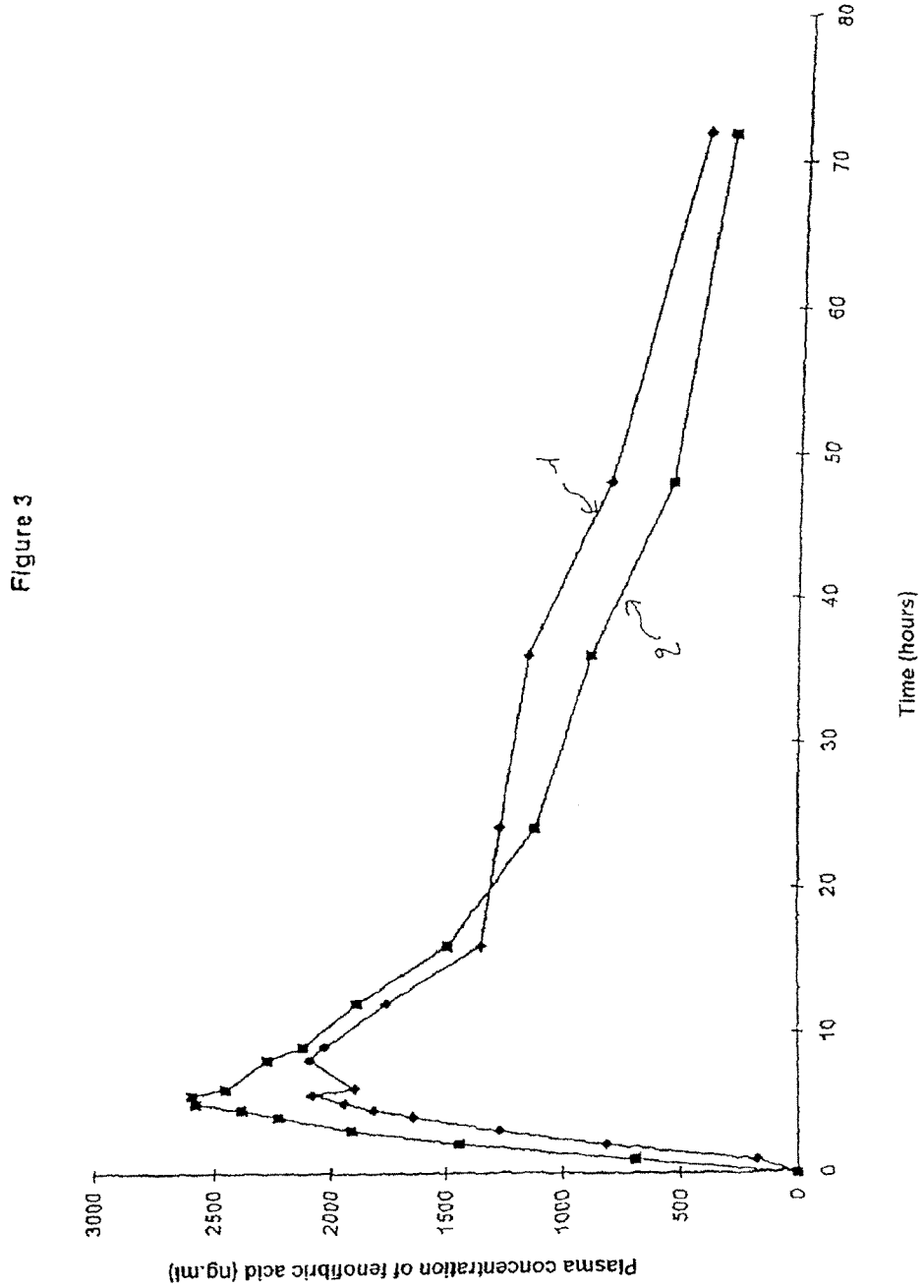
70
80
Time (hours)
2
1

Figure 2


Plasma concentration of fenofibric acid (ng.ml)
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2500
2000
1500
1000
500
0
0
10
20
30
40
50
60
70
80
Time (hours)
1
2

Figure 3

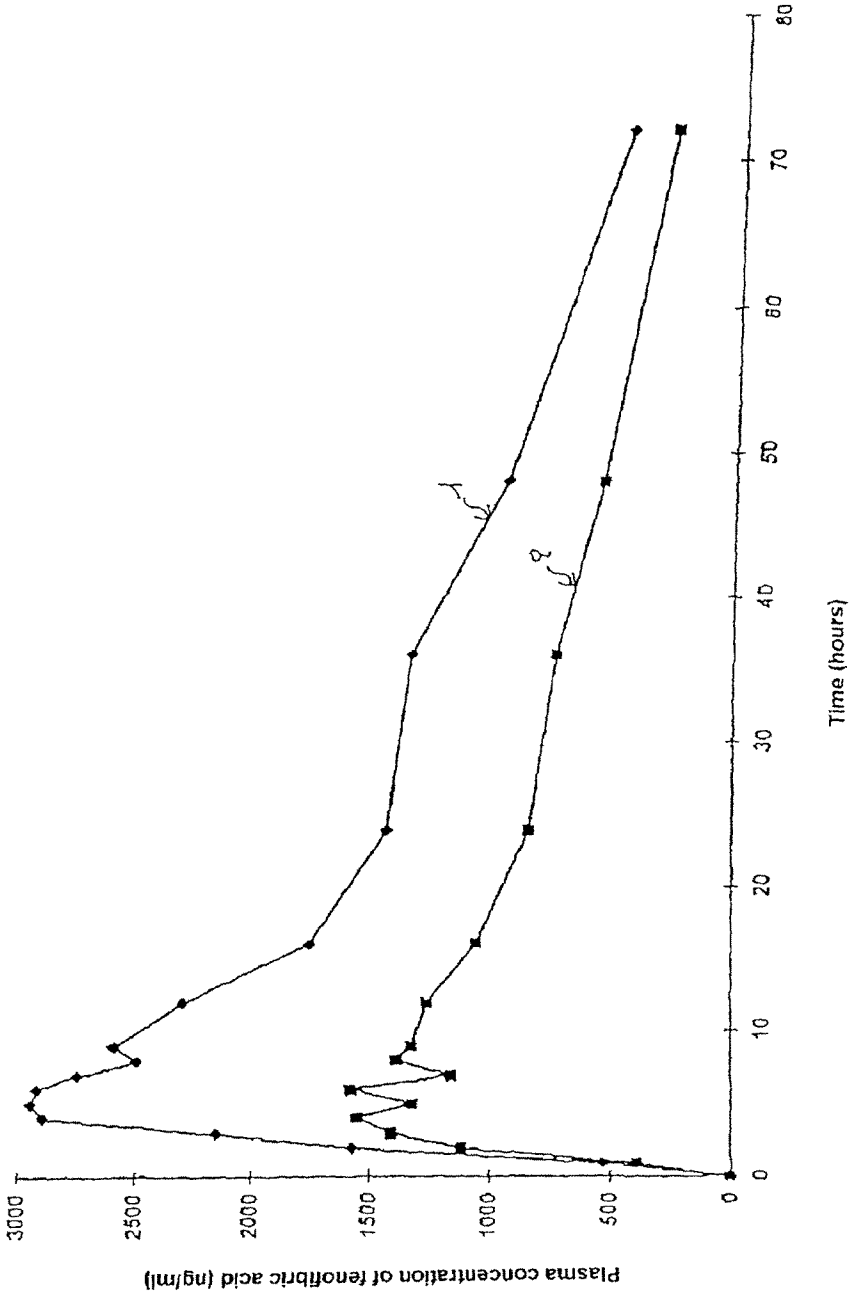
Plasma concentration of fenofibric acid (ng/ml)
3000
2500
2000
1500
1000
500
0
0
10
20
30
40
50
60
70
80
Time (hours)
1
2

Figure 4

PHARMACEUTICAL COMPOSITION CONTAINING FENOFIBRATE AND THE PREPARATION METHOD

This application is a 371 of PCT/FR00/01971 filed on Jul. 7, 2000.

The present invention relates to a novel pharmaceutical composition containing fenofibrate.

Fenofibrate is recommended in the treatment of adult endogenous hyperlipidemias, of hypercholesterolemias and of hypertriglyceridemias. A treatment of 300 to 400 mg of fenofibrate per day enables a 20 to 25% reduction of cholesterolemia and a 40 to 50% reduction of triglyceridemia to be obtained.

The major fenofibrate metabolite in the plasma is fenofibric acid. The half-life for elimination of fenofibric acid from the plasma is of the order of 20 hours. Its maximum concentration in the plasma is attained, on average, five hours after ingestion of the medicinal product. The mean concentration in the plasma is of the order of 15 micrograms/ml for a dose of 300 mg of fenofibrate per day. This level is stable throughout treatment.

Fenofibrate is an active principle which is very poorly soluble in water, and the absorption of which in the digestive tract is limited. An increase in its solubility or in its rate of solubilization leads to better digestive absorption.

Various approaches have been explored in order to increase the rate of solubilization of fenofibrate: micronization of the active principle, addition of a surfactant, and comicronization of fenofibrate with a surfactant.

Patent EP 256 933 describes fenofibrate granules in which the fenofibrate is micronized in order to increase its bioavailability. The crystalline fenofibrate microparticles are less than 50 μm in size. the binder used is polyvinylpyrrolidone. The document suggests other types of binder, such as methacrylic polymers, cellulose derivatives and polyethylene glycols. The granules described in the examples of EP 256 933 are obtained by a method using organic solvents.

Patent EP 330 532 proposes improving the bioavailability of fenofibrate by comicronizing it with a surfactant, such as sodium lauryl sulfate. The comicronizate is then granulated by wet granulation in order to improve the flow capacities of the powder and to facilitate the transformation into gelatin capsules. This comicronization allows a significant increase in the bioavailability compared to the use of fenofibrate described in EP 256 933. The granules described in EP 330 532 contain polyvinylpyrrolidone as a binder.

This patent teaches that the comicronization of fenofibrate with a solid surfactant significantly improves the bioavailability of the fenofibrate compared to the use of a surfactant, of micronization or of the combination of a surfactant and of micronized fenofibrate.

Patent WO 98/31361 proposes improving the bioavailability of the fenofibrate by attaching to a hydrodispersible inert support micronized fenofibrate, a hydrophilic polymer and, optionally, a surfactant. The hydrophilic polymer, identified as polyvinyl-pyrrolidone, represents at least 20% by weight of the composition described above.

This method makes it possible to increase the rate of dissolution of the fenofibrate, and also its bioavailability. However, the preparation method according to that patent is not entirely satisfactory since it requires the use of a considerable amount of PVP and of the other excipients. The example presented in that patent application refers to a composition containing only 17.7% of fenofibrate expressed as a mass ratio. This low mass ratio for fenofibrate leads to a final form which is very large in size, hence a difficulty in administering the desired dose of fenofibrate, or the administration of two tablets.

In the context of the present invention, it has been discovered that the incorporation of a cellulose derivative, used as a binder and solubilization adjuvant, into a composition containing micronized fenofibrate and a surfactant makes it possible to obtain a bioavailability which is greater than for a composition containing a comicronizate of fenofibrate and of a surfactant.

A subject of the present invention is therefore a pharmaceutical composition containing micronized fenofibrate, a surfactant and a binding cellulose derivative, which is a solubilization adjuvant, preferably hydroxypropylmethylcellulose (HPMC).

The composition of the invention is advantageously provided as gelatin capsules containing powder or granules, preferably in the form of granules. These granules may in particular be prepared by assembly on neutral microgranules, by spraying an aqueous solution containing the surfactant, the solubilized binding cellulose derivative and the micronized fenofibrate in suspension, or by wet granulation of powder, according to which the constituents, including in particular the micronized fenofibrate, the surfactant and the cellulose derivative, are granulated by wet granulation using an aqueous wetting solution, dried and calibrated.

The pharmaceutical composition according to the present invention has a high proportion of fenofibrate; it may therefore be provided in a formulation which is smaller in size than the formulations of the prior art, which makes this composition according to the invention easy to administer.

The amount of fenofibrate is greater than or equal to 60% by weight, preferably greater than or equal to 70% by weight, even more preferably greater than or equal to 75% by weight, relative to the weight of the composition.

In the context of the present invention, the fenofibrate is not comicronized with a surfactant. On the contrary, it is micronized alone and then combined with a surfactant and with the binding cellulose derivative, which is a solubilization adjuvant.

The surfactant is chosen from surfactants which are solid or liquid at room temperature, for example sodium lauryl sulfate, Polysorbate® 80 or Montane® 20, preferably sodium lauryl sulfate.

The fenofibrate/HPMC ratio is preferably between 5/1 and 15/1.

The surfactant represents between 1 and 10%, preferably between 3 and 5%, by weight relative to the weight of fenofibrate.

The binding cellulose derivative represents between 2 and 15%, preferably between 5 and 12%, by weight of the composition.

Hydroxypropylmethylcellulose is preferably chosen, the apparent viscosity of which is between 2.4 and 18 cP, and even more preferably between 2.4 and 3.6 cP, such as for example Pharmacoat 603®.

The mean size of the fenofibrate particles is less than 15 μm, preferably 10 μm, even more preferably less than 8 μm.

The composition of the invention may also contain at least one excipient such as diluents, for instance lactose, antifoaming agents, for instance DIMETHICONE and SIMETHICONE, or lubricants, for instance talc.

The pharmaceutical composition of the invention advantageously consists of granules in an amount equivalent to a dose of fenofibrate of between 50 and 300 mg, preferably equal to 200 mg.

The present invention also relates to a method for preparing the powder or the granules, the composition of which is described above. This method uses no organic solvent.

According to a first variant, the granules are prepared by assembly on neutral microgranules.

The neutral microgranules have a particle size of between 200 and 1 000 microns, preferably between 400 and 600 microns.

The assembly is carried out in a sugar-coating pan, in a perforated coating pan or in a fluidized airbed, preferably in a fluidized airbed.

The assembly of neutral microgranules is carried out by spraying an aqueous suspension containing the surfactant, the solubilized binding cellulose derivative, and the micronized fenofibrate in suspension.

According to a second variant, the granules are obtained by wet granulation of powder. The granulation enables the powders to be made dense and makes it possible to improve their flow properties. It also allows better preservation of the homogeneity, by avoiding the various constituents becoming unmixed.

The micronized fenofibrate, the surfactant, the cellulose derivative and, optionally, the other excipients are mixed, granulated, dried and then calibrated. The wetting solution may be water or an aqueous solution containing the binding cellulose derivative and/or the surfactant.

According to a particular embodiment, the fenofibrate and the other excipients are mixed in a planetary mixer. The wetting solution is added directly to the mixture. The wet mass obtained is granulated with an oscillating granulator, and then dried in an oven. The granules are obtained after passage over an oscillating calibrator.

BRIEF DESCRIPTION OF DRAWINGS

FIG. **1** represents the in vivo release profile of the formulation of example 1C and of a formulation of the prior art in fasting individuals.

FIG. **2** represents the in vivo release profile of the formulation of example 1C and of a formulation of the prior art in individuals who have just eaten.

FIG. **3** represents the in vivo release profile of the formulation of example 2B and of a formulation of the prior art in fasting individuals.

FIG. **4** represents the in vivo release profile of the formulation of comparative example 3 and of a formulation of the prior art in individuals who have just eaten.

The invention is illustrated in a nonlimiting way by the following examples.

EXAMPLE 1

Granules

1A) Microgranules (XFEN 1735)

The microgranules are obtained by spraying an aqueous suspension onto neutral cores. The composition is given in the following table:

Formula	Amount (percentage by mass)
Micronized fenofibrate	64.5
Neutral microgranules	21
HPMC (Pharmacoat 603 ®)	11.2
Polysorbate ® 80	3.3
Fenofibrate content	645 mg/g

The in vitro dissolution was determined according to a continuous flow cell method with a flow rate of 8 ml/min of sodium lauryl sulfate at 0.1 N. The percentages of dissolved product as a function of time, in comparison with a formulation of the prior art, Lipanthyl 200 M, are given in the following table.

Time (min)	15	30
Example 1A (% dissolved)	73	95
Lipanthyl 200 M (% dissolved)	47.3	64.7

Formulation 1A dissolves more rapidly than Lipanthyl 200 M.

1B) Microgranules (X FEN 1935)

The mean size of the fenofibrate particles is equal to 6.9±0.7 microns.

The microgranules are obtained by spraying an aqueous suspension onto neutral cores. The suspension contains micronized fenofibrate, sodium lauryl sulfate and HPMC.

The assembly is carried out in a Huttlin fluidized airbed (rotoprocess).

The formula obtained is given below.

FORMULA	AMOUNT (percentage by mass)
Micronized fenofibrate	65.2
Neutral microgranules	20.1
HPMC (Pharmacoat 603 ®)	11.4
Sodium lauryl sulfate	3.3
Fenofibrate content	652 mg/g

The size of the neutral microgranules is between 400 and 600 μm.

1C) Gelatin Capsules of Microgranules (Y FEN 001)

Microgranules having the following composition are prepared:

RAW MATERIALS	AMOUNT (percentage by mass)
Micronized fenofibrate	67.1
Neutral microgranules	17.2
Pharmacoat 603 ® (HPMC)	11.7
Sodium lauryl sulfate	3.3
35% dimethicone emulsion	0.2
Talc	0.5
Fenofibrate content	671 mg/g

according to the method described in paragraph 1A).

The microgranules obtained are distributed into size 1 gelatin capsules, each containing 200 mg of fenofibrate.

The in vitro dissolution is determined according to a continuous flow cell method with a flow rate of 8 ml/min of sodium lauryl sulfate at 0.1 N. The comparative results with a formulation of the prior art, Lipanthyl 200 M, are given in the following table.

Time (min)	15	30
Example 1C (% dissolved)	76	100
Lipanthyl 200 M (% dissolved)	47.3	64.7

Formula 1C dissolves more rapidly than Lipanthyl 200 M.

The gelatin capsules are conserved for 6 months at 40° C./75% relative humidity. The granules are stable under these accelerated storage conditions. In vitro dissolution tests (in continuous flow cells with a flow rate of 8 ml/min of sodium lauryl sulfate at 0.1 N) were carried out. The percentages of dissolved product as a function of time for gelatin capsules conserved for 1, 3 and 6 months are given in the following table.

	Conservation time		
Dissolution time (min)	1 month (% dissolved product)	3 months (% dissolved product)	6 months (% dissolved product)
5	25.1	23.0	20.1
15	71.8	65.6	66.5
25	95.7	88.7	91.0
35	104.7	98.7	98.2
45	106.4	100.2	99.1
55	106.7	100.5	99.5
65	106.8	100.6	99.7

The evolution of the content of active principle during storage is given in the following table.

Content (mg/gelatin Capsule) Conservation time			
0	1 month	3 months	6 months
208.6	192.6	190.8	211.7

Pharmacokinetic Study Carried Out in Fasting Individuals

The in vivo release profile of the gelatin capsules containing the YFEN 01 granules at a dose of 200 mg of fenofibrate is compared with that of the gelatin capsules marketed under the trademark Lipanthyl 200 M.

This study is carried out in 9 individuals. Blood samples are taken at regular time intervals and fenofibric acid is assayed.

The results are given in the following table and FIG. **1**.

Pharmacokinetic parameters	Lipanthyl 200 M	Example 1C
AUC_{0-t} (µg · h/ml)	76	119
AUC_{inf} (µg · h/ml)	96	137
C_{max} (µg/ml)	2.35	4.71
T_{max} (hours)	8.0	5.5
Ke (1/hour)	0.032	0.028
Elim ½ (hours)	26.7	24.9

The following abbreviations are used in the present application:

C_{max}: maximum concentration in the plasma,

T_{max}: time required to attain the Cmax,

$Elim_{1/2}$: plasmatic half-life,

AUC_{0-t}: area under the curve from 0 to t,

$AUC_{0-\infty}$: area under the curve from 0 to ∞,

Ke: Elimination constant.

The results obtained for Lipanthyl 200 M and for the product of example 1C are represented on FIG. **1** by curves **1** and **2**, respectively.

These results show that the composition according to the present invention has a bioavailability which is greater than that of Lipanthyl 200 M in fasting individuals.

Pharmacokinetic Study Carried Out in Individuals Who Have Just Eaten

The in vivo release profile of the gelatin capsules containing the YFEN 01 granules at a dose of 200 mg of fenofibrate is compared with that of the gelatin capsules marketed under the trademark Lipanthyl 200 M.

This study is carried out in 18 individuals. Blood samples are taken at regular time intervals and fenofibric acid is assayed.

The results are given in the following table and FIG. **2**.

Pharmacokinetic parameters	Lipanthyl 200 M	Example 1C
AUC_{0-t} (µg · h/ml)	244	257
AUC_{inf} (µg · h/ml)	255	270
C_{max} (µg/ml)	12	13
T_{max} (hours)	5.5	5.5
Ke (1/hour)	0.04	0.04
Elim ½ (hours)	19.6	19.3

The results obtained for Lipanthyl 200 M and for the product of example 1C are represented on FIG. **2** by curves **1** and **2**, respectively.

These results show that the composition according to the present invention is bioequivalent to that of Lipanthyl 200 M in individuals who have just eaten.

EXAMPLE 2

Powder

2A) Granules (X FEN 1992)

Granules having the following composition are prepared

FORMULA	PERCENTAGE BY MASS
Micronized fenofibrate	71
Lactose	21.5
HPMC (Pharmacoat 603 ®)	5
Sodium lauryl sulfate	2.5

The micronized fenofibrate, the HPMC and the lactose are mixed using a planetary mixer. This mixture is granulated in the presence of a solution of sodium lauryl sulfate.

The flow time of the granules is 7 s. The compacting capacity and the particle size distribution are given in the following tables. These measurements were carried out in accordance with the standards of the European Pharmacopoeia.

Compacting capacity (X FEN 1992)	
V0	204 ml
V10	186 ml
V500	168 ml
V1250	164 ml
V10–V500	22 ml

Particle size distribution (X FEN 1992)

Sieve mesh size (mm)	% of oversize mass
0.6	8
0.5	9
0.355	12
0.2	30
0.1	23
0	18

2B) Gelatin Capsules of Granules (Y FEN 002)

Preparation

The micronized fenofibrate is mixed in a PMA mixer (Niro Fielder) with lactose and HPMC, and then wetted with an aqueous solution of sodium lauryl sulfate. The mass obtained is granulated by passage over an oscillating granulator, dried and then calibrated on a sieve with a mesh size of 1.25 mm.

The granules are then packaged in size 1 gelatin capsules at doses of 200 mg of fenofibrate.

Granules of the following composition are obtained.

FORMULA	PERCENTAGE BY MASS
Micronized fenofibrate	70
Lactose	21.5
Pharmacoat 603 ® (HPMC)	5
Sodium lauryl sulfate	3.5
Content	700 mg/g

Properties of the Granules

The flow time of the granules is 6 s. The compacting capacity and the particle size distribution are given in the following tables. These measurements were carried out in accordance with the standards of the European Pharmacopoeia.

Compacting capacity (Y FEN 002)	
V0	216 ml
V10	200 ml
V500	172 ml
V1250	170 ml
V10–V500	28 ml

Particle size distribution (Y FEN 002)

Sieve mesh size (mm)	% of oversize mass
0.6	5
0.5	7

-continued

Particle size distribution (Y FEN 002)

Sieve mesh size (mm)	% of oversize mass
0.355	11
0.2	30
0.1	25
0	22

The in vitro dissolution is determined according to a continuous flow cell method with a flow rate of 8 ml/min of sodium lauryl sulfate at 0.1 N. The comparative results for a formulation of the prior art, Lipanthyl 200 M, are given in the following table.

Time (min)	15	30
Example 2B (% dissolved)	82.2	88.5
Lipanthyl 200 M (% dissolved)	47.3	64.7

Formulation 2B dissolves more rapidly than Lipanthyl 200 M.

Stability Tests

The gelatin capsules conserved at 40° C./75% relative humidity are stable for 6 months.

In vitro dissolution tests (in continuous flow cells with a flow rate of 8 ml/min of sodium lauryl sulfate at 0.1 N) were carried out. The percentages of dissolved product as a function of time for gelatin capsules conserved for 1, 3 and 6 months are given in the following table.

	Conservation time		
Dissolution time (min)	1 month (% dissolved product)	3 months (% dissolved product)	6 months (% dissolved product)
5	54.2	52.9	49.0
15	81.1	75.8	82.2
25	86.4	79.6	87.2
35	88.8	81.6	89.8
45	90.7	82.9	91.5
55	92.1	83.9	92.7
65	93.2	84.7	93.6

The evolution of the content of active principle during storage is given in the following table.

Content (mg/gelatin capsule)

Conservation time			
0	1 month	3 months	6 months
196.6	190.0	199.8	203.3

Pharmacokinetic Study Carried Out in Fasting Individuals

The in vivo release profile of the gelatin capsules containing the YFEN 002 granules at doses of 200 mg of fenofibrate is compared with that of the gelatin capsules marketed under the trademark Lipanthyl 200 M.

This study is carried out in 9 individuals. Blood samples are taken at regular time intervals and fenofibric acid is assayed.

The results are given in the following table and FIG. **3**.

Pharmacokinetic parameters	Lipanthyl 200 M	Example 1C
AUC_{0-t} (μg · h/ml)	76	70
AUC_{inf} (μg · h/ml)	96	62
C_{max} (μg/ml)	2.35	2.8
T_{max} (hours)	8.0	5.5
Ke (1/hour)	0.032	0.033
Elim ½ (hours)	26.7	23.1

The results obtained for Lipanthyl 200 M and for the product of example 2B are represented on FIG. **3** by curves **1** and **2**, respectively.

These results show that the composition of example 2B is bioequivalent to that of Lipanthyl 200 M in fasting individuals.

COMPARATIVE EXAMPLE 3

Batch ZEF 001

This example illustrates the prior art.

It combines micronization of fenofibrate and the use of a surfactant. It differs from the present invention by the use of the mixture of binding excipients consisting of a cellulose derivative other than HPMC: Avicel PH 101 and polyvinylpyrrolidone (PVP K30).

It is prepared by extrusion-spheronization.

Theoretical Formula

Products	Theoretical amount (%)
Micronized fenofibrate	75.08
Montanox 80 ®	4.72
Avicel PH 101 ®	5.02
PVP K 30 ®	4.12
Explotab ®	11.06

In Vitro Dissolution Profile

The in vitro dissolution is determined according to a continuous flow cell method with a flow rate of 8 ml/min of sodium lauryl sulfate at 0.1 N. The comparative results with Lipanthyl 200 M are given in the following table.

Time (min)	15	30
Example 3 (% dissolved)	24	40
Lipanthyl 200 N (% dissolved)	47.3	647

The dissolution is slower than that observed for Lipanthyl 200 M.

Pharmacokinetic Study Carried Out in Fasting Individuals

The in vivo release profile of the gelatin capsules containing the ZEF 001 granules at doses of 200 mg of fenofibrate is compared with that of the gelatin capsules marketed under the trademark Lipanthyl 200 M.

This study is carried out in 5 fasting individuals receiving a single dose. Blood samples are taken at regular time intervals and fenofibric acid is assayed.

The results are given in the following table and FIG. **4**.

Pharmacokinetic parameters	Lipanthyl 200 M	Example 3
AUC_{0-t} (μg · h/ml)	92	47
AUC_{inf} (μg · h/ml)	104	53
C_{max} (μg/ml)	3.5	1.7
T_{max} (hours)	5.6	4.6
Ke (1/hour)	0.04	0.038
Elim ½ (hours)	18.9	20.3

The results obtained for Lipanthyl 200 M and for the product of example 3 are represented on FIG. **4** by curves **1** and **2**, respectively.

These results show the greater bioavailability of Lipanthyl 200 M compared with this formulation based on the prior art.

Example 3 shows that combining the knowledge of the prior art (namely micronization or use of surfactants) does not make it possible to obtain rapid dissolution of fenofibrate. This results in low bioavailability compared with Lipanthyl 200 M.

The compositions prepared according to the present invention show more rapid dissolution than the formula of the prior art and improved bioavailability.

The invention claimed is:

1. A pharmaceutical composition in the form of granules, wherein each granule comprises a neutral microgranule on which is a composition comprising: micronized fenofibrate, a surfactant, and a binding cellulose derivative as a solubilization adjuvant, and

wherein said fenofibrate is present in an amount greater than or equal to 60% by weight, relative to the weight of said pharmaceutical composition, and further wherein said binding cellulose derivative represents between 2 to 15% by weight, relative to the weight of said pharmaceutical composition.

2. The pharmaceutical composition of claim **1**, wherein said binding cellulose derivative is hydroxypropylmethylcellulose (HPMC).

3. The pharmaceutical composition of claim **2**, wherein said hydroxypropylmethylcellulose has an apparent viscosity of between 2.4 and 18 cP.

4. The pharmaceutical composition of claim **1**, wherein said fenofibrate is present in an amount greater than or equal to 70% by weight, relative to the weight of said pharmaceutical composition.

5. The pharmaceutical composition of claim **1**, wherein said surfactant is selected from the group consisting of polyoxyethylene 20 sorbitan monooleate, sorbitan monododecanoate, and sodium lauryl sulfate.

6. The pharmaceutical composition of claim **1**, wherein said surfactant represents between 1 and 10% by weight, relative to the weight of said fenofibrate.

7. The pharmaceutical composition of claim **2**, wherein said fenofibrate/HPMC mass ratio is between 5/1 and 15/1.

8. The pharmaceutical composition of claim **1**, wherein said pharmaceutical composition further comprises at least one excipient.

9. The pharmaceutical composition of claim **1**, wherein said micronized fenofibrate has a mean particle size less than 15 μm.

10. The pharmaceutical composition of claim **1**, wherein said composition is contained in gelatin capsules.

11. A method for preparing the pharmaceutical composition of claim **1**, wherein said granules are prepared by

spraying onto neutral microgranules an aqueous suspension of micronized fenofibrate containing surfactant and solubilized binding cellulose derivative.

12. The pharmaceutical composition of claim **3**, wherein said hydroxypropylmethylcellulose has an apparent viscosity of between 2.4 and 3.6 cP.

13. The pharmaceutical composition of claim **1**, wherein said fenofibrate is present in an amount greater than or equal to 75% by weight, relative to the weight of said pharmaceutical composition.

14. The pharmaceutical composition of claim **1**, wherein said surfactant represents between 3 and 5% by weight, relative to the weight of said fenofibrate.

15. The pharmaceutical composition of claim **1**, wherein said binding cellulose derivative represents between 5 and 12% by weight, relative to the weight of said pharmaceutical composition.

16. The pharmaceutical composition of claim **8**, wherein said excipient is selected from the group consisting of a diluent, an antifoaming agent, a lubricant, and a mixture thereof.

17. The pharmaceutical composition of claim **8**, wherein said excipient is selected from the group consisting of lactose, α-(trimethylsilyl)-ω-methylpoly[oxy-(dimethylsilylene)], a mixture of α-(trimethylsilyl)-ω-methylpoly[oxy-(dimethylsilylene)] with silicon dioxide, and talc.

18. The pharmaceutical composition of claim **1**, wherein said micronized fenofibrate has a mean particle size less than 8 μm.

19. A pharmaceutical composition in the form of granules, wherein each granule comprises a neutral microgranule on which is a composition comprising: micronized fenofibrate, a surfactant, and a binding cellulose derivative as a solubilization agent, wherein the mass ratio of said fenofibrate to said binding cellulose derivative is between 5/1 and 15/1.

20. The pharmaceutical composition according to claim **19**, wherein said binding cellulose derivative is hydroxypropylmethylcellulose.

21. The pharmaceutical composition of claim **19**, wherein said binding cellulose derivative has an apparent viscosity of between 2.4 and 18 cP.

22. The pharmaceutical composition of claim **19**, wherein said binding cellulose derivative has an apparent viscosity of between 2.4 and 3.6 cP.

23. The pharmaceutical composition of claim **19**, wherein said surfactant is selected from the group consisting of polyoxyethylene 20 sorbitan monooleate, sorbitan monododecanoate, and sodium lauryl sulfate.

24. The pharmaceutical composition of claim **19**, wherein said surfactant represents between 1 and 10% by weight, relative to the weight of said fenofibrate.

25. The pharmaceutical composition of claim **19**, wherein said surfactant represents between 3 and 5% by weight, relative to the weight of said fenofibrate.

26. The pharmaceutical composition of claim **19**, wherein said pharmaceutical composition further comprises at least one excipient.

27. The pharmaceutical composition of claim **26**, wherein said excipient is selected from the group consisting of a diluent, an antifoaming agent, a lubricant, and a mixture thereof.

28. The pharmaceutical composition of claim **27**, wherein said diluent is lactose.

29. The pharmaceutical composition of claim **27**, wherein said antifoaming agent is α-(trimethylsilyl)-ω-methylpoly[oxy-(dimethylsilylene)] or a mixture of α-(trimethylsilyl)-ω-methylpoly[oxy-(dimethylsilylene)] with silicon dioxide.

30. The pharmaceutical composition of claim **27**, wherein said lubricant is talc.

31. The pharmaceutical composition of claim **19**, wherein said micronized fenofibrate has a mean particle size less than 15 μm.

32. The pharmaceutical composition of claim **19**, wherein said micronized fenofibrate has a mean particle size less than 8 μm.

33. The pharmaceutical composition of claim **19**, wherein said composition is contained in gelatin capsules.

34. The pharmaceutical composition of claim **2**, wherein at least 95% of said fenofibrate is dissolved at 30 minutes, as measured using a continuous flow cell method with a flow rate of 8 ml/min of sodium lauryl sulfate at 0.1 N.

* * * * *

EXHIBIT 2

US007863331B2

(12) **United States Patent**
Criere et al.

(10) **Patent No.: US 7,863,331 B2**
(45) **Date of Patent: *Jan. 4, 2011**

(54) **PHARMACEUTICAL COMPOSITION CONTAINING FENOFIBRATE AND METHOD FOR THE PREPARATION THEREOF**

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(73) Assignee: **Ethypharm**, Saint Cloud (FR)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 1259 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **10/677,861**

(22) Filed: **Oct. 3, 2003**

(65) **Prior Publication Data**

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Related U.S. Application Data

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(30) **Foreign Application Priority Data**

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A61K 31/19 (2006.01)
A61K 9/20 (2006.01)

(52) **U.S. Cl.** **514/571**; 424/465

(58) **Field of Classification Search** 514/571; 424/465

See application file for complete search history.

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(57) **ABSTRACT**

Pharmaceutical compositions comprising micronized fenofibrate, a surfactant and a binding cellulose derivative as a solubilization adjuvant, wherein said compositions contain an amount of fenofibrate greater than or equal to 60% by weight and methods of producing fenofibrate compositions.

4 Claims, 5 Drawing Sheets

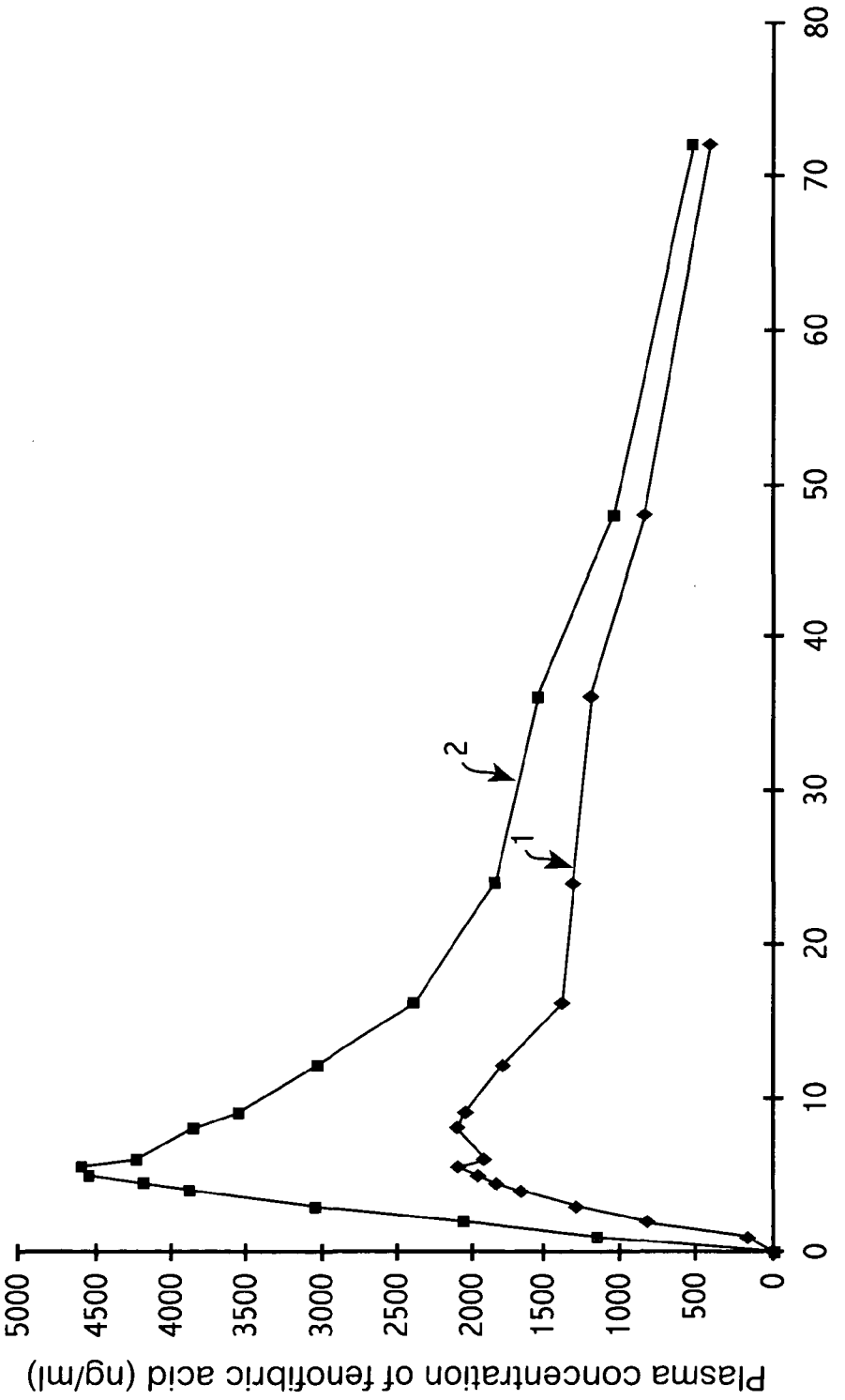
Plasma concentration of fenofibric acid (ng/ml)
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
0
10
20
30
40
50
60
70
80
Time (hours)
1
2

FIG. 1

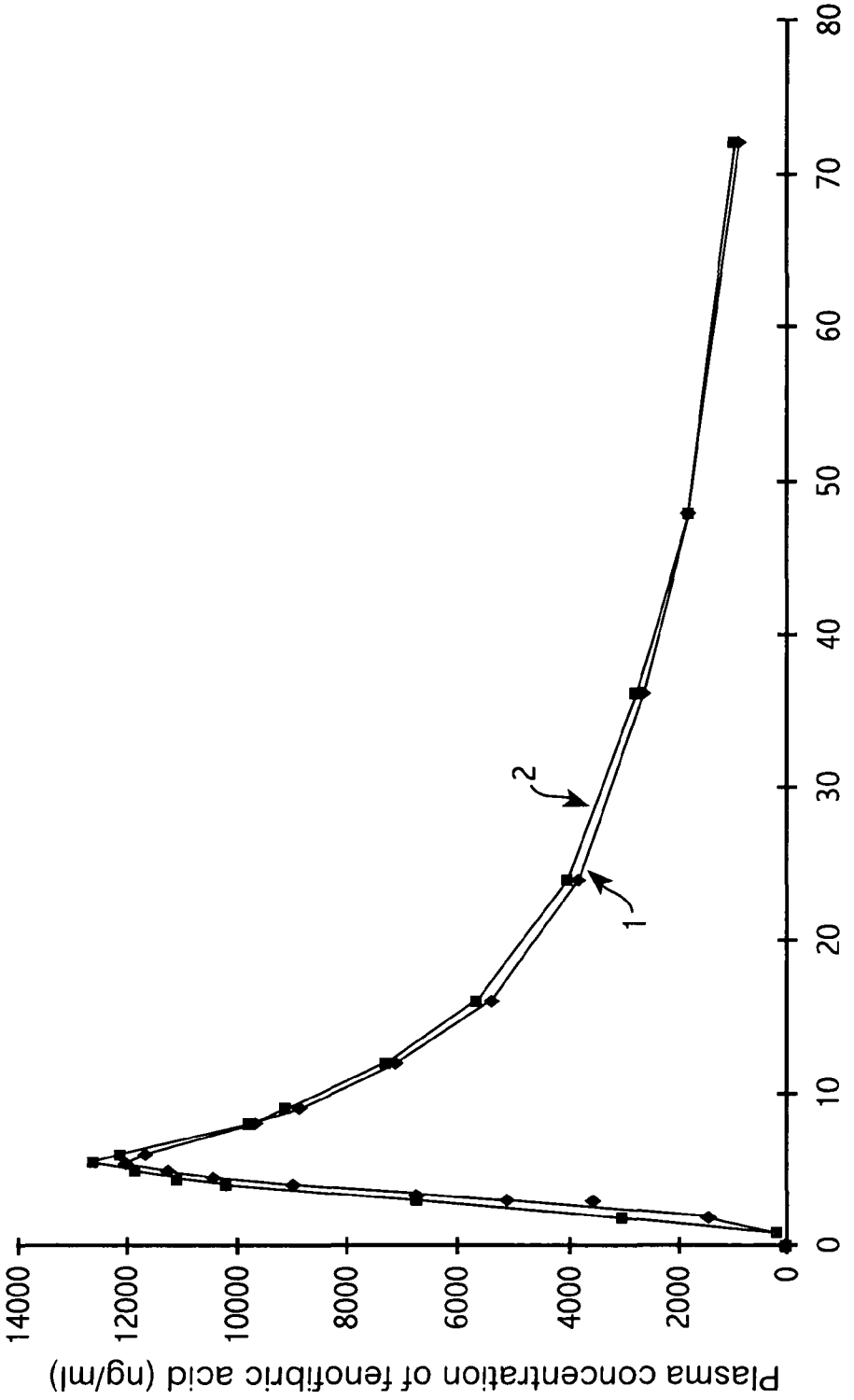
Plasma concentration of fenofibric acid (ng/ml)
14000
12000
10000
8000
6000
4000
2000
0
0
10
20
30
40
50
60
70
80
Time (hours)
1
2

FIG. 2

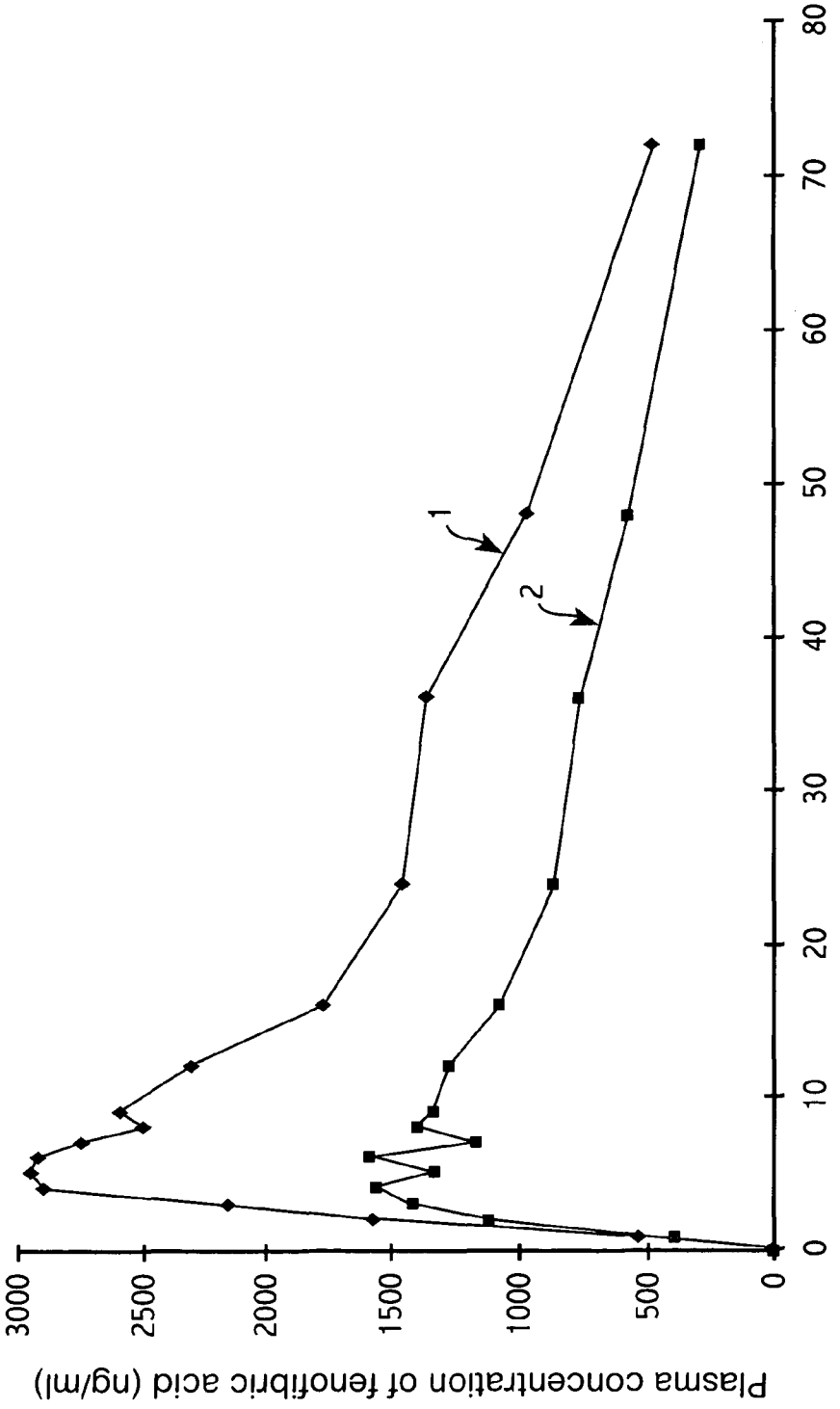
Plasma concentration of fenofibric acid (ng/ml)
3000
2500
2000
1500
1000
500
0
0
10
20
30
40
50
60
70
80
Time (hours)
1
2

FIG. 3

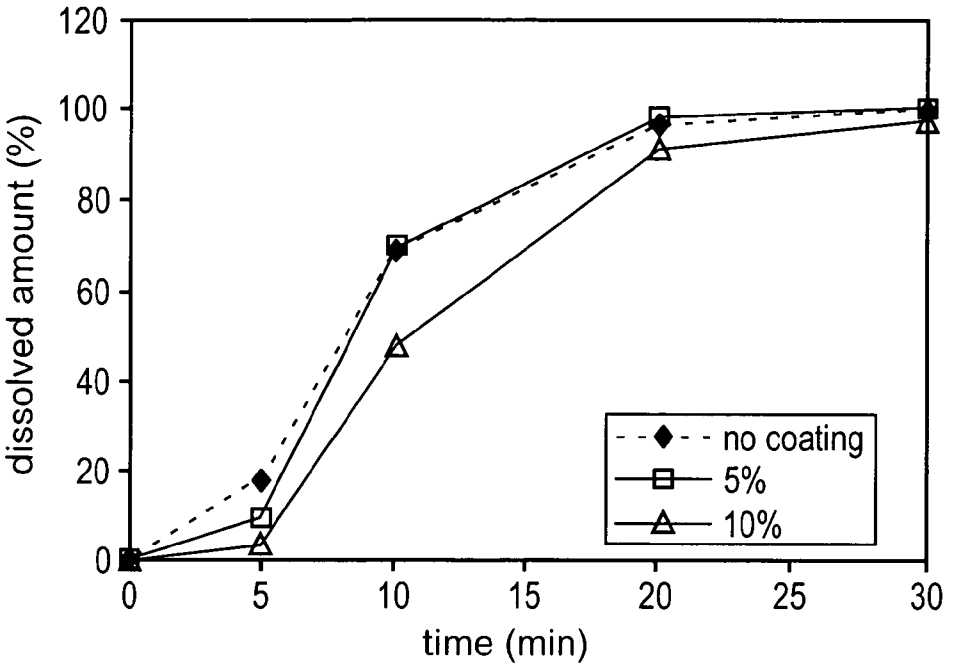
120
100
80
60
40
20
0
dissolved amount (%)
0
5
10
15
20
25
30
time (min)
no coating
5%
10%

FIG. 4

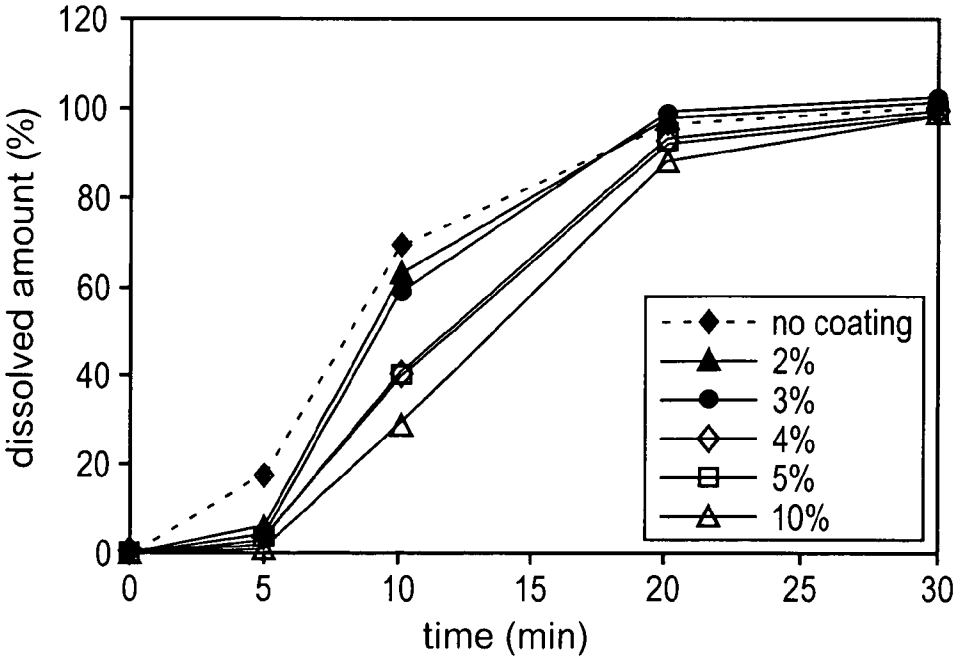
120
100
80
60
40
20
0
dissolved amount (%)
0
5
10
15
20
25
30
time (min)
no coating
2%
3%
4%
5%
10%

FIG. 5

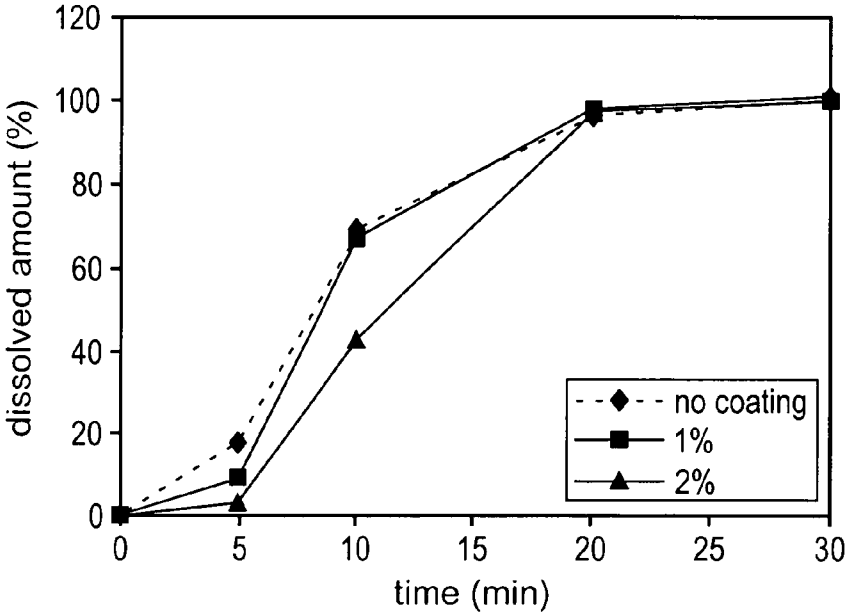
dissolved amount (%)
120
100
80
60
40
20
0
0
5
10
15
20
25
30
time (min)
no coating
1%
2%

FIG. 6

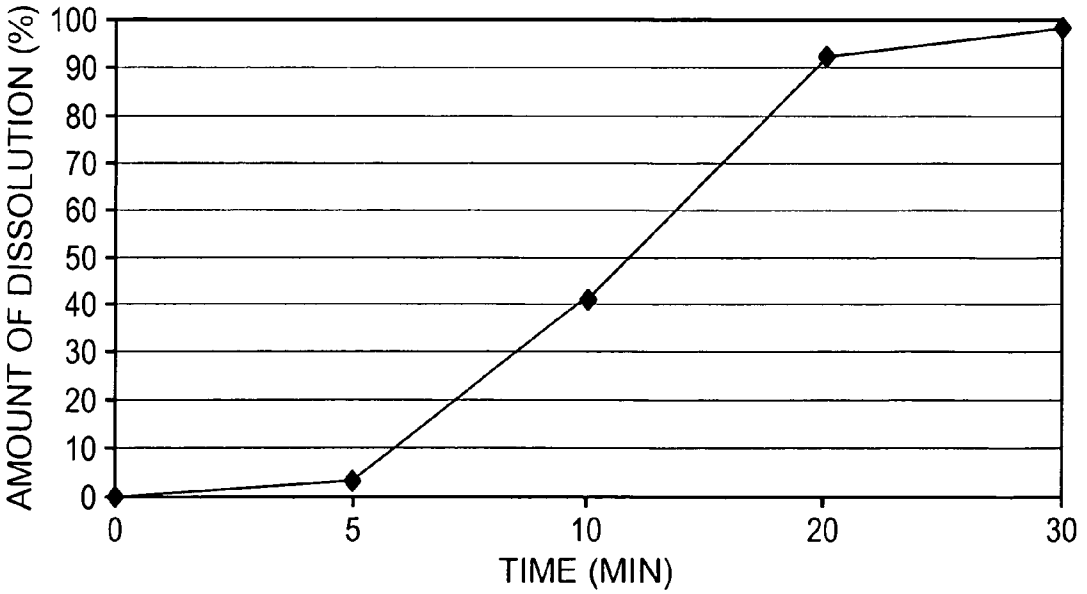
AMOUNT OF DISSOLUTION (%)
100
90
80
70
60
50
40
30
20
10
0
0
5
10
20
30
TIME (MIN)

FIG. 7

PHARMACEUTICAL COMPOSITION CONTAINING FENOFIBRATE AND METHOD FOR THE PREPARATION THEREOF

FIELD OF THE INVENTION

The present invention relates to a novel pharmaceutical composition containing fenofibrate.

BACKGROUND OF THE INVENTION

Fenofibrate is recommended in the treatment of adult endogenous hyperlipidemias, of hypercholesterolemias and of hypertriglyceridemias. A treatment of 300 to 400 mg of fenofibrate per day enables a 20 to 25% reduction of cholesterolemia and a 40 to 50% reduction of triglyceridemia to be obtained.

The major fenofibrate metabolite in the plasma is fenofibric acid. The half-life for elimination of fenofibric acid from the plasma is of the order of 20 hours. Its maximum concentration in the plasma is attained, on average, five hours after ingestion of the medicinal product. The mean concentration in the plasma is of the order of 15 micrograms/ml for a dose of 300 mg of fenofibrate per day. This level is stable throughout treatment.

Fenofibrate is an active principle which is very poorly soluble in water, and the absorption of which in the digestive tract is limited.

Due to its poor affinity for water and to its hydrophobic nature, fenofibrate is much better absorbed after ingestion of food, than in fasting conditions. This phenomenon called "food effect" is particularly important when comparing fenofibrate absorption in high fat meal conditions versus fasting conditions.

The main drawback in this food effect is that food regimen must be controlled by the patient who is treated with fenofibrate, thereby complicating the compliance of the treatment. Yet, as fenofibrate is better absorbed in high fat meal conditions, it is usually taken after a fat meal. Therefore, these conditions of treatment are not adapted to patients treated for hyperlipidemia or hypercholesterolemia who must observe a low fat regimen.

A way to limit the food effect is to increase the solubility or the rate of solubilization of fenofibrate, thereby leading to a better digestive absorption, whichever the food regimen.

DESCRIPTION OF THE RELATED ART

Various approaches have been explored in order to increase the rate of solubilization of fenofibrate: micronization of the active principle, addition of a surfactant, and comicronization of fenofibrate with a surfactant.

Patent EP 256 933 describes fenofibrate granules in which the fenofibrate is micronized in order to increase its bioavailability. The crystalline fenofibrate microparticles are less than 50 μm in size. The binder used is polyvinylpyrrolidone. The document suggests other types of binder, such as methacrylic polymers, cellulose derivatives and polyethylene glycols. The granules described in the examples of EP 256 933 are obtained by a method using organic solvents.

Patent EP 330 532 proposes improving the bioavailability of fenofibrate by comicronizing it with a surfactant, such as sodium lauryl sulfate. The comicronizate is then granulated by wet granulation in order to improve the flow capacities of the powder and to facilitate the transformation into gelatin capsules. This comicronization allows a significant increase in the bioavailability compared to the use of fenofibrate described in EP 256 933. The granules described in EP 330 532 contain polyvinylpyrrolidone as a binder.

This patent teaches that the comicronization of fenofibrate with a solid surfactant significantly improves the bioavailability of the fenofibrate compared to the use of a surfactant, of micronization or of the combination of a surfactant and of micronized fenofibrate.

Patent WO 98/31361 proposes improving the bioavailability of the fenofibrate by attaching to a hydrodispersible inert support micronized fenofibrate, a hydrophilic polymer and, optionally, a surfactant. The hydrophilic polymer, identified as polyvinylpyrrolidone, represents at least 20% by weight of the composition described above.

This method makes it possible to increase the rate of dissolution of the fenofibrate, and also its bioavailability. However, the preparation method according to that patent is not entirely satisfactory since it requires the use of a considerable amount of PVP and of the other excipients. The example presented in that patent application refers to a composition containing only 17.7% of fenofibrate expressed as a mass ratio. This low mass ratio for fenofibrate leads to a final form which is very large in size, hence a difficulty in administering the desired dose of fenofibrate, or the administration of two tablets.

DETAILED DESCRIPTION OF THE INVENTION

In the context of the present invention, it has been discovered that the incorporation of a cellulose derivative, used as a binder and solubilization adjuvant, into a composition containing micronized fenofibrate and a surfactant makes it possible to obtain a bioavailability which is greater than for a composition containing a comicronizate of fenofibrate and of a surfactant. It has further been discovered the pharmaceutical composition of the present invention makes it possible to obtain comparable bioavailability to prior art formulations containing a higher dosage of micronized fenofibrate.

More particularly, it has been observed that bioavailability of fenofibrate is increased when microgranules according to the present invention are prepared by mixing together in a liquid phase the fenofibrate, the surfactant and the binding cellulose derivative before spraying this liquid phase onto neutral cores.

Indeed, both cellulose derivative and surfactant are dissolved in the liquid phase in which the microparticles of micronized fenofibrate are in suspension.

Thus, when the solvent is removed from the suspension by evaporation after spraying onto neutral cores, molecules of both cellulose derivative and surfactant are adsorbed directly onto the fenofibrate microparticles. This phenomenon induces a very homogeneous repartition and creates a very close contact between fenofibrate microparticles and these molecules, which are responsible for its better solubilization in the gastro-intestinal fluids and thereby allow a better absorption of fenofibrate, also contributing to a reduction of the food effect as mentioned above.

Thus, it has been discovered that the pharmaceutical composition of the present invention has less food effect than prior art formulations when administered to patient, i.e. the inventive formulation is less dependent on the presence of food in the patient to achieve high bioavailability. For example, prior art fenofibrate formulations must be taken with food to achieve high bioavailability. The inventors have unexpectedly discovered a fenofibrate composition that achieves high bioavailability almost independent of the presence of food in a patient.

Finally, it has been discovered that the addition of an outer layer of a hydrosoluble binder results in a novel in vivo profile, with the following limits: less than 10% in 5 minutes and more than 80% in 20 minutes, as measured using the rotating blade method at 75 rpm according to the European Pharmacopoeia, in a dissolution medium constituted by water with 2% by weight polysorbate 80 or in a dissolution medium constituted by water with 0.025M sodium lauryl sulfate.

A subject of the present invention is therefore a pharmaceutical composition containing micronized fenofibrate, a surfactant and a binding cellulose derivative, that become intimately associated after the removing of the solvent used in the liquid phase.

The composition of the invention is advantageously provided as gelatin capsules containing granules. These granules may in particular be prepared by assembly on neutral cores, by spraying an aqueous solution containing the surfactant, the solubilized binding cellulose derivative and the micronized fenofibrate in suspension.

For example, the pharmaceutical composition of the present invention may include a composition in the form of granules comprising:

(a) a neutral core; and

(b) an active layer, which surrounds the neutral core;

wherein said neutral core may include lactose, mannitol, a mixture of sucrose and starch or any other acceptable sugar, and wherein said active layer comprises the micronized fenofibrate, the surfactant and the binding cellulose derivative.

Or, for example, the pharmaceutical composition of the present invention may include an immediate release fenofibrate composition including (a) a neutral core; (b) an active layer, which surrounds the core; and (c) an outer layer; wherein the active layer comprises micronized fenofibrate, a surfactant and a binding cellulose derivative.

The pharmaceutical composition according to the present invention has a high proportion of fenofibrate; it may therefore be provided in a formulation which is smaller in size than the formulations of the prior art, which makes this composition according to the invention easy to administer. Further, the pharmaceutical composition of the present invention provides comparable bioavailability to prior art formulations at higher dosage strengths of fenofibrate. Thus, the inventive composition provides advantages over prior art formulations. For example, the inventive formulation containing only 130 mg of fenofibrate has comparable bioavailability with a prior art formulation containing 200 mg of fenofibrate under fed or fasted conditions, and with single or multiple dosing.

The amount of fenofibrate is greater than or equal to 60% by weight, preferably greater than or equal to 70% by weight, even more preferably greater than or equal to 75% by weight, relative to the weight of the composition.

In the context of the present invention, the fenofibrate is not comicronized with a surfactant. On the contrary, it is micronized alone and then combined with a surfactant and with the binding cellulose derivative, which is a solubilization adjuvant.

The surfactant is chosen from surfactants which are solid or liquid at room temperature, for example sodium lauryl sulfate, Polysorbate® 80 (polyoxyethylene 20 sorbitan monooleate), Montane® 20 or sucrose stearate, preferably sodium lauryl sulfate.

The fenofibrate/HPMC ratio is preferably between 5/1 and 15/1.

The surfactant represents between about 1 and 10%, preferably between about 3 and 5%, by weight relative to the weight of fenofibrate.

The binding cellulose derivative represents between about 2 and 20%, preferably between 5 and 12%, by weight of the composition.

Hydroxypropylmethylcellulose is preferably chosen, the apparent viscosity of which is between 2.4 and 18 cP, and even more preferably between about 2.4 and 3.6 cP, such as for example Pharmacoat 603®.

The mean size of the fenofibrate particles is less than 15 μm, preferably 10 μm, even more preferably less than 8 μm.

The composition of the invention may also contain at least one excipient such as diluents, for instance lactose, antifoaming agents, for instance Dimethicone® (α-(trimethylsilyl)-γ-methylpoly[oxy(dimethylsilylene)]) and Simethicone® (mixture of α-(trimethylsilyl)-γ-methylpoly[oxy(dimethylsilylene)] with silicon dioxide), or lubricants, for instance talc or colloidal silicon dioxide such as Aerosil®.

The antifoaming agent may represent between about 0 and 10%, preferably between about 0.01 and 5%, even more preferably between about 0.1 and 0.7%, by weight of the composition.

The lubricant may represent between about 0 and 10%, preferably between about 0.1 and 5%, even more preferably between about 0.2 and 0.6%, by weight of the composition.

The composition of the invention may also include a outer coating or layer of a hydrosoluble binder. The hydrosoluble binder of the outer layer represents between about 1 and 15%, preferably between about 1 and 8%, even more preferably between about 2-4% by weight of the composition. The hydrosoluble binder may include hydroxypropylmethylcellulose, polyvinylpyrrolidone, or hydroxypropylcellulose or a mixture thereof. However, one of ordinary skill in the art would understand other substances that may be used as the hydrosoluble binder in the outer layer.

Hydroxypropylmethylcellulose is preferably chosen, the apparent viscosity of which is between 3 and 15 cP, such as for example Pharmacoat 606®, or a mixture of different grades varying in viscosity. The amount of HPMC in the outer layer is inversely proportional to viscosity. It is within the skill in the art to determine the amount of hydrosoluble binder to obtain the claimed properties in the dissolution profile.

The outer layer may also include one or more excipient such as lubricants, for instance talc. The lubricant may represent between about 0 and 10%, preferably between about 1 and 5%, even more preferably between about 1-2%, by weight of the composition.

The pharmaceutical composition of the invention advantageously consists of granules in an amount equivalent to a dose of fenofibrate of between 50 and 300 mg, preferably between 130 and 200 mg and more preferably equal to 200 mg.

These granules preferably comprise:

(a) a neutral core;

(b) an active layer, which surrounds the core; and

(c) an outer layer.

The expression "outer layer" means an outer coating which is applied on the neutral core (A) coated with the active layer (B). Said coating may consist of one or several layers.

The outer layer may comprise a hydrosoluble binder.

The hydrosoluble binder of the outer layer may include hydroxypropylmethylcellulose, polyvinylpyrrolidone, or hydroxypropylcellulose. However, one of ordinary skill in the art would understand other substances that may be used as the binding cellulose derivative in the outer layer.

In the outer layer, hydroxypropylmethylcellulose is preferably chosen among Hydroxypropylmethylcellulose having an apparent viscosity of 3 cP, such as Pharmacoat 603®, or 6 cP, such as Pharmacoat 606®, or 15 cP such as Pharmacoat 615®.

The outer layer may further comprise talc. In that case, the HPMC/talc mass ratio is preferably comprised between 1/1 and 5/1.

The present invention also relates to a pharmaceutical composition of fenofibrate that can be administered to provide substantial reduction of an effect of food on the uptake of the fenofibrate, i.e. substantial reduction of the food effect.

Such a pharmaceutical composition presents the advantage of being almost independent of the food conditions. Such a composition substantially reduces or eliminates the difference of bioavailability observed in function of the nature of the meal and between fed and fasted conditions.

Indeed, food can change the bioavailability of a drug, which can have clinically significant consequences. Food can alter bioavailability by various means, including: delaying gastric emptying, stimulating bile flow, changing gastrointestinal (GI) pH, increasing splanchnic blood flow, changing luminal metabolism of a drug substance, and physically or chemically interacting with a dosage form or a drug substance. Food effects on bioavailability are generally greatest when the drug product is administered shortly after a meal is ingested, such as provided in prior art fenofibrate formulations. The nutrient and caloric contents of the meal, the meal volume, and the meal temperature can cause physiological changes in the GI tract in a way that affects drug product transit time, luminal dissolution, drug permeability, and systemic availability. In general, meals that are high in total calories and fat content are more likely to affect the GI physiology and thereby result in a larger effect on the bioavailability of a drug substance or drug product. Notably, fenofibrate is prescribed for cholesterol management to patients who cannot eat high fat foods. Thus, there is a need for a fenofibrate composition that need not be administered with high fat foods. The present invention, unlike prior art fenofibrate formulation, achieves high bioavailability irrespective of the presence of food.

Accordingly, a method of reducing food effect is provided when treating hyperlipidemias, hypercholesterolemias and hypertriglyceridemias in a patient, including the steps of administering to the patient an effective amount of the instant invention. Further, the bioavailability of the composition is equivalent whether the patient is fed a high fat meal, a therapeutic lifestyle change diet, or when the patient is fasted.

In addition, the invention provides a composition comprising fenofibrate having a novel in vivo dissolution profile of less than 10% in 5 minutes and more than 80% in 20 minutes, as measured using the rotating blade method at 75 rpm according to the European Pharmacopoeia, in a dissolution medium constituted by water with 2% by weight polysorbate 80 or in a dissolution medium constituted by water with 0.025M sodium lauryl sulfate.

The composition according to the present invention, advantageously has a dissolution profile less than 5% at 5 minutes and more than 90% at 20 minutes, as measured using the rotating blade method at 75 rpm according to the European Pharmacopeia in a dissolution medium constituted by water with 0.25M sodium lauryl sulfate.

The present invention also relates to a method for preparing the granules, the composition of which is described above. This method uses no organic solvent.

The granules are prepared by assembly on neutral cores.

The neutral cores have a particle size of between 200 and 1000 microns, preferably between 400 and 600 microns. The neutral cores may represent between about 1 and 50%, preferably between about 10 and 20%, even more preferably between about 14-18%, by weight of the composition.

The assembly is carried out in a sugar-coating pan, in a perforated coating pan or in a fluidized airbed, preferably in a fluidized airbed.

The assembly on neutral cores is carried out by spraying an aqueous solution containing the surfactant, the solubilized binding cellulose derivative, and the micronized fenofibrate in suspension, and then optionally, by spraying an aqueous solution containing the the hydrosoluble binder.

The invention is illustrated in a non limiting way by the following examples

BRIEF DESCRIPTION OF THE DRAWING FIGURES

FIG. **1** represents the in vivo release profile of the formulation of example 1C and of a formulation of the prior art in fasting individuals. (Curve 1: Lipanthyl® 200M; Curve 2: composition according to the present invention).

FIG. **2** represents the in vivo release profile of the formulation of example 1C and of a formulation of the prior art in individuals in fed condition. (Curve 1: Lipanthyl® 200M; Curve 2: composition according to the present invention).

FIG. **3** represents the in vivo release profile of the formulation of comparative example 2 and of a formulation of the prior art in individuals in fed condition.

FIG. **4** represents the in vitro dissolution profile as a function of the amount of the (HPMC 603/Talc) suspension applied on the microgranules.

FIG. **5** represents the in vitro dissolution profile as a function of the amount of the (HPMC 606/Talc) suspension applied on the microgranules.

FIG. **6** represents the in vitro dissolution profile as a function of the amount of the (HPMC 615/Talc) suspension applied on the microgranules.

FIG. **7** represents the in vitro dissolution profile as a function of the amount of the (HPMC 606/Talc) 4% suspension applied on the microgranules.

EXAMPLES

Although the present invention has been described in detail with reference to examples above, it is understood that various modifications can be made without departing from the spirit of the invention, and would be readily known to the skilled artisan. Additionally, the invention is not to be construed to be limited by the following examples.

Example 1

Granules

1A) Microgranules (XFEN 1735)

The microgranules are obtained by spraying an aqueous suspension of micronized fenofibrate onto neutral cores. The composition is given in the following table:

Formula	Amount (percentage by mass)
Micronized fenofibrate	64.5
Neutral cores	21

-continued

Formula	Amount (percentage by mass)
HPMC (Pharmacoat 603 ®)	11.2
Polysorbate ® 80	3.3
Fenofibrate content	645 mg/g

The in vitro dissolution was determined according to a continuous flow cell method with a flow rate of 8 ml/min of sodium lauryl sulfate at. 0.1 N. The percentages of dissolved product as a function of time, in comparison with a formulation of the prior art, 15 Lipanthyl 200 M, are given in the following table.

	Time (min)	
	15	30
Example 1A (% dissolved)	73	95
Lipanthyl 200 M (% dissolved)	47.3	64.7

Formulation 1A dissolves more rapidly than Lipanthyl 200 M.

1B) Microgranules (X FEN 1935)

The mean size of the fenofibrate particles is equal to 6.9±0.7 microns.

The microgranules are obtained by spraying an aqueous suspension onto neutral cores. The suspension contains micronized fenofibrate, sodium lauryl sulfate and HPMC. The assembly is carried out in a Huttlin fluidized airbed (rotoprocess).

The formula obtained is given below.

FORMULA	AMOUNT (percentage by mass)
Micronized fenofibrate	65.2
Neutral cores	20.1
HPMC (Pharmacoat 603 ®)	11.4
Sodium lauryl sulfate	3.3
Fenofibrate content	652 mg/g

The size of the neutral cores is between 400 and 600 μm.

1C) Gelatin Capsules of Microgranules (Y FEN 001)

Microgranules having the following composition are prepared:

RAW MATERIALS	AMOUNT (percentage by mass)
Micronized fenofibrate	67.1
Neutral cores	17.2
Pharmacoat 603 ® (HPMC)	11.7
Sodium lauryl sulfate	3.3
35% dimethicone emulsion	0.2
Talc	0.5
Fenofibrate content	671 mg/g

according to the method described in paragraph 1A).

The microgranules obtained are distributed into size 1 gelatin capsules, each containing 200 mg of fenofibrate.

The in vitro dissolution is determined according continuous flow cell method with a flow rate of 8 ml/min of sodium lauryl sulfate at 0.1 N. The comparative results with a formulation of the prior art, Lipanthyl 200 M, are given in the following table.

	Time (min)	
	15	30
Example 1C (% dissolved)	76	100
Lipanthyl 200 M (% dissolved)	47.3	64.7

Formula 1C dissolves more rapidly than Lipanthyl 200 M.

The gelatin capsules are conserved for 6 months at 40° C./75% relative humidity. The granules are stable under these accelerated storage conditions. In vitro dissolution tests (in continuous flow cells with a flow rate of 8 ml/min of sodium lauryl sulfate at 0.1 N) were carried out. The percentages of dissolved product as a function of time for gelatin capsules conserved for 1, 3 and 6 months are given in the following table.

	Conservation time		
Dissolution time (min)	1 month (% dissolved product)	3 months (% dissolved product)	6 months (% dissolved product)
5	25.1	23.0	20.1
15	71.8	65.6	66.5
25	95.7	88.7	91.0
35	104.7	98.7	98.2
45	106.4	100.2	99.1
55	106.7	100.5	99.5
65	106.8	100.6	99.7

The evolution of the content of active principle during storage is given in the following table.

	Conservation time			
	0	1 month	3 months	6 months
Content (mg/gelatin Capsule)	208.6	192.6	190.8	211.7

Pharmacokinetic Study Carried Out in Fasting Individuals

The in vivo release profile of the gelatin capsules containing the example 1C granules at a dose of 200 mg of fenofibrate is compared with that of the gelatin capsules marketed under the trademark Lipanthyl 200 M.

This study is carried out in 9 individuals. Blood samples are taken at regular time intervals and fenofibric acid is assayed.

The results are given in the following table and FIG. **1**.

Pharmacokinetic parameters	Lipanthyl 200 M	Example 1C
AUC_{o-t} (μg · h/ml)	76	119
AUC_{inf} (μg · h/ml)	96	137
C_{max} (μg/ml)	2.35	4.71
T_{max} (hours)	8.0	5.5
Ke (1/hour)	0.032	0.028
Elim ½ (hours)	26.7	24.9

The following abbreviations are used in the present application:

C_{max}: maximum concentration in the plasma,

T_{max}: time required to attain the C_{max},

Elim ½: plasmatic half-life,

AUC_{0-t}: area under the curve from 0 to t,

$AUC_{0-\infty}$: area under the curve from 0 to ∞,

Ke: Elimination constant.

The results obtained for Lipanthyl 200 M and for the product of example 1C are represented on FIG. **1** by curves 1 and 2, respectively.

These results show that the composition according to the present invention has a bioavailability which is greater than that of Lipanthyl 200 M in fasting individuals.

Pharmacokinetic Study Carried Out in Individuals in Fed Condition

The in vivo release profile of the gelatin capsules containing the example 1C granules at a dose of 200 mg of fenofibrate is compared with that of the gelatin capsules marketed under the trademark Lipanthyl 200 M.

This study is carried out in 18 individuals. Blood samples are taken at regular time intervals and fenofibric acid is assayed.

The results are given in the following table and FIG. **2**.

Pharmacokinetic parameters	Lipanthyl 200 M	Example 1C
AUC_{o-t} (µg · h/ml)	244	257
AUC_{inf} (µg · h/ml)	255	270
C_{max} (µg/ml)	12	13
T_{max} (hours)	5.5	5.5
Ke (1/hour)	0.04	0.04
Elim ½ (hours)	19.6	19.3

The results obtained for Lipanthyl 200 M and for the product of example 1C are represented on FIG. **2** by curves 1 and 2, respectively.

These results show that the composition according to the present invention is bioequivalent to that of Lipanthyl 200 M in individuals in fed condition.

Comparison of the Pharmacokinetic in Individuals Under Fed Condition Versus the Pharmacokinetic in Fasting Individuals

Under fasted conditions it was unexpectedly found that the formulation of the invention provided a statically significant increased relative bioavailability of approximately 1.4 times that of the Lipanthyl® as evidenced by a 100% higher mean maximum concentration (C_{max}) of the drug and approximately 62% higher mean AUC's. This significant difference between the two formulations disappeared under fed condition.

When the bioavailability of the Lipanthyl® under fed versus fasted conditions was compared, the C_{max} significantly increased (418%) and the mean AUC's significantly increased by (152%).

In contrast, when the bioavailability of the formulation of this invention under fed versus fasted conditions was compared, the C_{max} significantly increased by only 170% and the mean AUC'S were increased only by 76%.

The formulation according to the invention provides a pharmacokinetic profile in which the effect of ingestion of food on the uptake of the drug is substantially reduced over that observed with Lipanthyl®.

Comparative Example 2

Batch ZEF 001

This example illustrates the prior art.

It combines micronization of fenofibrate and the use of a surfactant. It differs from the present invention by the use of the mixture of binding excipients consisting of a cellulose derivative other than HPMC: Avicel PH 101 and polyvinylpyrrolidone (PVP K30).

It is prepared by extrusion-spheronization.

Theoretical formula

Products	Theoretical amount %
Micronized fenofibrate	75.08
Montanox 80 ®	4.72
Avicel PH 101 ®	5.02
PVP K 30 ®	4.12
Explotab ®	11.06

In vitro dissolution profile

The in vitro dissolution is determined according to a continuous flow cell method with a flow rate of 8 ml/min of sodium lauryl sulfate at 0.1 N. The comparative results with Lipanthyl 200 M are given in 10 the following table.

	Time (min)	
	15	30
Example 2 (% dissolved)	24	40
Lipanthyl 200 M (% dissolved)	47.3	64.7

The dissolution is slower than that observed for Lipanthyl 200 M.

Pharmacokinetic Study Carried Out in Fasting Individuals

The in vivo release profile of the gelatin capsules containing the ZEF 001 granules at doses of 200 mg of fenofibrate is compared with that of the gelatin capsules marketed under the trademark Lipanthyl 200 M.

This study is carried out in 5 fasting individuals receiving a single dose. Blood samples are taken at regular time intervals and fenofibric acid is assayed.

The results are given in the following table and FIG. **3**.

Pharmacokinetic Parameters	Lipanthyl 200 M	Example 2
AUC_{o-t} (µg · h/ml)	92	47
AUC_{inf} (µg · h/ml)	104	53
C_{max} (µg/ml)	3.5	1.7
T_{max} (hours)	5.6	4.6
Ke (1/hour)	0.04	0.038
Elim ½ (hours)	18.9	20.3

The results obtained for Lipanthyl 200 M and for the product of example 2 are represented on FIG. **3** by curves 1 and 2, respectively.

These results show the greater bioavailability of Lipanthyl 200 M compared with this formulation based on the prior art.

Example 2 shows that combining the knowledge of the prior art (namely micronization or use of surfactants) does not

make it possible to obtain rapid dissolution of fenofibrate. This results in low bioavailability compared with Lipanthyl 200 M.

The compositions prepared according to the present invention show more rapid dissolution than the formula of the prior art and improved bioavailability.

Example 3

Microgranules Coated with an Outer Layer

Microgranules were prepared by spraying an aqueous suspension onto neutral cores.

The composition of the suspension is given in the following table:

Suspension	Amount (percentage by mass)
Purified water	78.09
35% dimethicone emulsion	0.19
30% simethicone emulsion	0.03
HydroxyPropylMethylCellulose (HPMC) 2910 (Pharmacoat ® 603)	3.31
Sodium lauryl sulphate	0.89
Micronized fenofibrate	17.49
Total	100.00

The composition of the obtained microgranule is given in the following table:

Formula of microgranules	Amount (kg)
Micronized fenofibrate	372.00
Sugar spheres	96.00
HydroxyPropylMethylCellulose (HPMC) 2910 (Pharmacoat ® 603)	70.32
Sodium lauryl sulphate	18.96
35% dimethicone emulsion	4.12
30% simethicone emulsion	0.67
Talc	2.72
Purified water	1660.80

Different additional outer layers composed of a suspension of HPMC and talc (2:1, w:w) were applied on the obtained microgranules. They differ from each other:

- by the type of HPMC used: Pharmacoat® 603, 606 or 615. The major difference between these HPMC is their viscosity which increases in the order HPMC 603<HPMC 606<HPMC 615.
- by the amount of the (HPMC/Talc) suspension applied on the microgranules: 1, 2, 3, 4, 5 or 10%, expressed as dry HPMC/talc relative to the total microgranule.

Dissolution tests were performed with hand-filled gelatine capsules. The mass of microgranules introduced in the capsule was calculated according to the theoretical content of fenofibrate in the formula.

The equipment was composed of:

- a dissolutest (for example: SOTAX AT7 type),
- a pump which allows direct sample analysis,
- a UV spectrophotometer (for example: Lambda 12 from Perkin Elmer).

The dissolution method used was a rotating blade method at 75 rpm according to the European Pharmacopoeia.

The dissolution medium was composed of water with 0.025 M sodium lauryl sulfate. The temperature was set at 37.0° C.±0.5° C.

Dissolution profile as a function of the amount of the (HPMC/Talc) suspension applied on the microgranules

The effect exerted on the dissolution profile by the amount of the HPMC/Talc suspension applied on the microgranules was studied. The results are summarized on FIGS. **4** to **6** for HPMC 603, 606 and 615 respectively.

The coating leads to the apparition of a delay after 5 min dissolution.

Example 4

Microgranules Coated with an Outer Layer Applied by Spraying a (HPMC 606/Talc) 4% Suspension

Microgranules are obtained by spraying an aqueous suspension of micronized fenofibrate prepared as described in example 3 onto neutral cores, followed by an outer layer of HPMC and talc, the composition of the microgranules is given in the following table:

FORMULA	PERCENTAGE BY MASS
Neutral cores	16.44
Micronized fenofibrate	63.69
Hydroxypropylmethyl cellulose 3.0 Viscosity cP	12.04
Sodium lauryl sulfate	3.25
Dimethicone	0.25
Simethicone	0.03
Talc	0.63
Outer layer	
Hydroxypropylmethyl cellulose 6.0 Viscosity cP	2.57
Talc	1.1

Example 5

Dissolution Profile

A dissolution profile for a fenofibrate composition prepared according to example 4 was carried out by rotating blade method at 75 rpm, according to the European Pharmacopoeia. The dissolution medium was composed of water with 0.025 M sodium lauryl sulfate. The temperature was set at 37° C.±0.5° C.

The vessel was filled with 1000 mL sodium lauryl sulfate 0.025 M. One hand-filled capsules were added to the vessel. The test sample was taken at time intervals of 5 minutes (during 1 hour) and analyzed at a wavelength of 290 nm, through 2 mm quartz cells, against a blank constituted of 0.025 M sodium lauryl sulfate. The results obtained are shown graphically in FIG. **7**, on which the percentage of dissolution is shown and in the following table.

Time (min)	Amount of dissolution (%)
5	3 ± 1
10	41 ± 7
20	92 ± 4
30	98 ± 1

These results clearly show that the composition according to the invention has a dissolution profile which is less than 10% in five minutes and more than 80% in 20 minutes.

Example 6

A comparison of the relative bioavailability of 130 mg fenofibrate composition prepared according to example 4 and Tricor® 200 mg under fasted conditions and following consumption of a standard high fat FDA test meal in healthy adult subjects.

A test of bioavailability on healthy volunteers was carried out. The following compositions were tested: capsules containing microgranules prepared according to example 4 containing 130 mg of fenofibrate and Tricor® from Abbott Laboratories, containing 200 mg of fenofibrate. The study was carried out on 32 healthy volunteers in a randomized, single-dose, open-label (laboratory blinded), 4-way crossover study to determine the relative bioavailability under fasted and fed conditions in healthy adult subjects. The relative bioavailability of each formulation under fasted and fed conditions was also assessed. Subjects randomized to treatment A received a single oral dose of 130 mg fenofibrate prepared according to example 4 taken with 240 mL of tap water following a 10-hour fast. Subjects randomized to Treatment B received a single oral dose of the same formulation taken with 240 mL of tap water following a standardized high-fat meal. Subjects randomized to Treatment C received a single oral dose of one Tricor® (fenofibrate) 200 mg micronized capsule taken with 240 mL of tap water following a 10-hour fast. Subjects randomized to Treatment D received a single oral dose of one Tricor® (fenofibrate) 200 mg micronized capsule taken with 240 mL of tap water following a standardized high-fat meal.

In these examples, "fasted" is based on a 10-hour absence of food, however, a skilled artisan would know other methods of preparing fasted conditions. For example, "fasted" may be understood as 10 hour or more absence of food.

The standardized high-fat meal contains approximately 50 percent of total caloric content of the meal from fat or a calorie content of 800-1000 calories of which 50 percent is from fat. An example of the standardized high-fat meal is two eggs fried in butter, two strips of bacon, two slices of toast with butter, four ounces of hash brown potatoes (fired with butter) and eight ounces of whole milk. Substitutions in this test meal can be made as long as the meal provides a similar amount of calories from protein, carbohydrate, and fat and has comparable meal volume and viscosity. The results obtained are given in Tables 1 and 2 below:

TABLE 1

Pharmacokinetic Parameters for Fenofibric Acid Following a Single Dose Under Fasted and Fed (Standard High-Fat FDA Test Meal) Conditions

Parameter	Treatment A Invention 130 mg (Fasted)	Treatment B Invention 130 mg (Fed)	Treatment C Tricor ® 200 mg (Fasted)	Treatment D Tricor ® 200 mg (Fed)
AUC_{0-t} (ng · h/mL)	114853	145562	109224	224330
AUC_{0-inf} (ng · h/mL)	116134	146843	111235	226004
C_{max} (ng/mL)	4375	9118	3413	12829
T_{max} (h)	4.84	4.89	9.61	5.65
$t_{1/2}$ (h)	19.7	18.3	21.0	19.0

TABLE 2

Fed vs Fasted Ratios for Individual Formulations

Parameter	B: Invention 130 mg (Fed) vs A: Invention 130 mg (Fasted)	D: Tricor ® 200 mg (Fed) vs C: Tricor ® 200 mg (Fasted)
AUC_{0-t}	124.8	221.1
AUC_{0-inf}	124.6	218.8
C_{max}	210.2	434.2

Table 1 shows that the extent of absorption (AUC) of fenofibric acid following administration of 130 mg fenofibrate of the invention is comparable to that of the Tricor® 200 mg capsule under fasted conditions.

In addition, table 2 shows that the maximum plasma concentration (C_{max},) for the invention is lower than Tricor®, indicating that food effected the rate of bioavailability for the Tricor® formulation. Specifically, the food effect observed for the invention is approximately 2-fold lower than that observed for the Tricor® 200 mg capsule. This suggests that the rate of bioavailability for the invention is almost independent of the presence of food. In contrast, the rate of bioavailability for Tricor® significantly increased with food.

Example 7

A comparison of the relative bioavailability of 130 mg fenofibrate composition prepared according to in example 4 versus Tricor® 200 mg capsules at steady state in healthy adult subjects on a Therapeutic Lifestyle Change Diet ("TLC").

A test of bioavailability on healthy volunteers was carried out. The following compositions were tested: capsules containing microgranules prepared according to example 4 containing 130 mg of fenofibrate and Tricor® from Abbott Laboratories, containing 200 mg of fenofibrate. The study was carried out on 28 healthy volunteers in a randomized, multiple-dose, open-label (laboratory-blinded), 2-way crossover study to determine and compare the bioavailability of the formulation prepared according to example 4 of the invention relative to Tricor® 200 mg oral capsules immediately following consumption of a TLC diet meal. Subjects randomized to Treatment A received a single oral dose of one 130 mg capsule of the invention taken with 240 mL of room temperature tap water daily for 7 days. Subjects randomized to Treatment B received a single oral dose of one Tricor® (fenofibrate) 200 mg micronized capsule taken with 240 mL of room temperature tap water daily for 7 days.

The TLC Diet stresses reductions in saturated fat and cholesterol intake. The TLC diet contains approximately 25-30 percent fat per meal. An example of a TLC meals is 1 cup of bran cereal, 1 cup of fat free milk, 8 ounces of orange juice, 1 small banana, 1 slice whole wheat toast, 1 teaspoon of margarine, and coffee, black or with fat free milk. Substitutions in this test meal can be made as long as the meal provides a similar amount of calories from protein, carbohydrate, and fat and has comparable meal volume and viscosity. The results obtained are given in Table 3 below:

TABLE 3

Pharmacokinetic Parameters for Fenofibric Acid Following Multiple Dosing in Healthy Subjects on a TLC Diet

Parameter	Treatment A Invention 130 mg (Fed)	Treatment B Tricor ® 200 mg (Fed)
$AUC_{\tau, ss}$ (ng · h/mL)	182889	204988
$C_{max, ss}$ (ng/mL)	12664	13810
$T_{max, ss}$ (h)	4.896	5.343
$C_{av, ss}$ (ng/mL)	7620	8541
$C_{min, ss}$ (ng/mL)	4859	5878

The results on table 3 show that the bioavailability of the capsules of the invention and the Tricor® 200 mg capsules are comparable after multiple dosing, immediately following consumption of a TLC diet meal.

Example 8

A Comparison of the Relative Bioavailability of 130 mg fenofibrate composition prepared according to example 4 and Tricor® 200 mg Under Fasted Conditions and Following Consumption of a Therapeutic Lifestyle Change Meal in Healthy Adult Subjects.

A test of bioavailability on healthy volunteers was carried out. The following compositions were tested: capsules containing microgranules prepared according to example 4 containing 130 mg of fenofibrate and Tricor® from Abbott Laboratories, containing 200 mg of fenofibrate. The study was carried out on 32 healthy volunteers in a randomized, single-dose, open-label (laboratory blinded), 4-way crossover study to determine the relative bioavailability of 130 mg of the invention prepared according example 4 to Tricor® 200 mg oral capsules under fasted and fed conditions in healthy adult subjects. The relative bioavailability of each formulation under fasted and fed conditions was also assessed. Subjects randomized to Treatment A received a single oral dose of 130 mg fenofibrate prepared according to example 4 taken with 240 mL tap water under fasted conditions. Subjects randomized to Treatment B received a single oral dose of 130 mg fenofibrate prepared according to example 4 formulation taken with 240 mL of room temperature tap water following a TLC meal. Subjects randomized to Treatment C received a single oral dose of one Tricor® 200 mg capsule taken with 240 mL tap water under fasted conditions. Subjects randomized to Treatment D received a single oral dose of one Tricor® 200 mg capsule taken with 240 mL of tap water following a TLC diet meal.

The results obtained are given in Tables 4 and 5 below:

TABLE 4

Pharmacokinetic Parameters for Fenofibric Acid Following a Single Dose Under Fasted and Fed (Therapeutic Lifestyle Change Meal) Conditions

Parameter	Treatment A: Invention 130 mg (Fasted)	Treatment B: Invention 130 mg (Fed)	Treatment C: Tricor ® 200 mg (Fasted)	Treatment D: Tricor ® 200 mg (Fed)
AUC_{0-t} (ng · h/mL)	126031	130400	123769	159932
AUC_{0-inf} (ng · h/mL)	128020	132387	129798	162332

TABLE 4-continued

Pharmacokinetic Parameters for Fenofibric Acid Following a Single Dose Under Fasted and Fed (Therapeutic Lifestyle Change Meal) Conditions

Parameter	Treatment A: Invention 130 mg (Fasted)	Treatment B: Invention 130 mg (Fed)	Treatment C: Tricor ® 200 mg (Fasted)	Treatment D: Tricor ® 200 mg (Fed)
C_{max} (ng/mL)	4403	7565	2734	7554
T_{max} (h)	4.73	4.21	8.37	4.58

TABLE 5

Fed vs. Fasted Ratios for Individual Formulations

Parameter	B: Invention 130 mg (Fed) vs A: Invention 130 mg (Fasted)	D: Tricor ® 200 mg (Fed) vs C: Tricor ® 200 mg (Fasted)
AUC_{0-t}	104.0	131.4
AUC_{0-inf}	103.9	127.9
C_{max}	175.1	279.7

The results on Table 4 show that following the consumption of a TLC meal, the maximum plasma concentration (C_{max}) of fenofibric acid and the extent of absorption (AUC) of the invention is comparable to Tricor®. Similarly, under fasted conditions, the extent of absorption (AUC) of the invention is comparable to Tricor®. But, the maximum plasma concentration (C_{max}) of fenofibric acid is greater for the invention than for the Tricor® formulation indicating that the invention is more easily absorbed.

Also, the results on Table 5 show that the consumption of a TLC meal effected the maximum plasma concentration (C_{max}) for both the invention and Tricor®. But the food effect is more than 2-fold lower for the invention as compared to Tricor®. This indicates that the rate of bioavailability for the invention is almost independent of the presence of food. In contrast, the rate of bioavailability for Tricor® significantly increased with food.

What is claimed is:

1. A method of reducing food effect when treating hypertriglyceridemias and/or hypercholesterolemias and/or hyperlipidemias in a patient in need thereof comprising administering to said patient a therapeutically effective amount of a pharmaceutical composition comprising micronized fenofibrate, a surfactant and hydroxypropylmethylcellulose, wherein said composition is in the form of granules comprising:

(a) a neutral core; and

(b) an active layer, surrounding the neutral core;

wherein said neutral core comprises a sugar or a sugar mixed with starch; said active layer comprises the micronized fenofibrate, the surfactant, and the binding cellulose derivative; and wherein the mass ratio of said fenofibrate to said hydroxypropylmethylcellulose is between 5/1 and 15/1, and said hydroxypropylmethylcellulose represents between 5 and 12% by weight of the composition.

2. The method of claim **1**, wherein said patient is fed a high fat containing meal and the bioavailability of fenofibrate administered to said patient is equivalent to when said patient has fasted.

3. The method of claim **1**, wherein said patient is fed at least 800-1000 calories, 50% of which are from fat, and the bioavailability of fenofibrate administered to said patient is equivalent to when said patient has fasted.

4. The method of claim **1**, wherein said patient is fed a therapeutic lifestyle change diet and the bioavailability of fenofibrate administered to said patient is equivalent to when said patient has fasted.

* * * * *

EXHIBIT 3

United States Patent [19]

Boyer

[11] **Patent Number: 4,800,079**

[45] **Date of Patent: Jan. 24, 1989**

[54] **MEDICINE BASED ON FENOFIBRATE, AND A METHOD OF PREPARING IT**

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[52] **U.S. Cl.** **424/482;** 424/490

[58] **Field of Search** 424/482, 490

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Attorney, Agent, or Firm—Sughrue, Mion, Zinn, Macpeak & Seas

[57] **ABSTRACT**

A granular medicine based on fenofibrate, each granule comprising an inert core, a layer based on fenofibrate, and a protective layer, the medicine being characterized in that the fenofibrate in the layer based on fenofibrate is present in the form of crystalline microparticles of dimensions not greater than 30 microns, and preferably less than 10 microns.

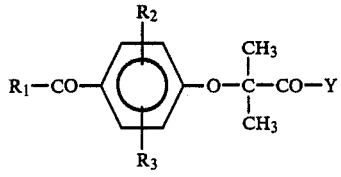
7 Claims, No Drawings

MEDICINE BASED ON FENOFIBRATE, AND A METHOD OF PREPARING IT

The present invention relates to a medicine based on fenofibrate, and also to a method of preparing it.

BACKGROUND OF THE INVENTION

It is recalled that fenofibrate is isopropyl para-(4-chlorobenzoyl)-pehnoxyisobutyrate. In the present application, the term "fenofibrate and its derivatives" is used to designate compounds having formula I:



(I)

in which:

R_1 represents a phenyl group or a phenyl group substituted by one or more —CH_3, CF_3 or by halogens (in particular fluorine, chlorine, or bromine);

R_2 and R_3 independently represent a hydrogen atom or a halogen atom (preferably fluorine, chlorine, or bromine), an alkyl or an alkoxy group having 1 to 5C or one of the following groups: —CF_3, —SCH_3, —$SOCH_3$, —SO_2CH_3, or —OH; and

Y represents one of the following groups: —OH; inferior alkoxy, preferably in C_1–C_4; —NR_4R_5; —$NHCH_2CH_2NR_4R_5$; or —O-alkylene-NR_4R_5, with the alkylene having, in particular, two to six atoms of carbon, and with R_4 and R_5 being identical or different and each representing a hydrogen atom or one of the following groups: C_1–C_5 alkyl, C_3–C_7 and preferably C_5–C_6 cycloalkyl; aryl or aryl substituted on the aromatic residue by one or more halogen, methyl, or —CF_3 groups; or else R_4 and R_5 constitute, together with the nitrogen atom to which they are connected, one fo the following groups: either an n-heterocyclic group having 5 to 7 vertices capable of enclosing a second hetero-atom selected from N, O, and S, and capable of being substituted; or else an amide residue derived from lysine or cysteine.

Naturally, the expression "fenofibrate and its derivatives" also covers the salts that can be obtained from compounds of formula I by adding pharmaceutically acceptable acids.

Fenofibrate is used in the treatment of adult endogenous hyperlipidaemia, hypercholesterolaemia, and hypertrigylceridaemia. Thus, in an adult being treated with 300 to 400 mg per day of fenofibrate, there can be observed a 20% to 25% reduction in chlolesterolaemia and a 40% to 50% reduction in triglyceridaemia.

The unaltered substance is not found in plasma. The major plasmatic metabolite is fenofibric acid.

On average, the maximum concentration in plasma is reached five hours after taking the medicine. The average concentration in plasma is about 50 micrograms/ml for a dose of 300 mg of fenofibrate per day. This level is stable throughout continuous treatment.

Fenofibric acid is strongly bound to plasmatic albumin and can displace antivitamins K from protein fixing sites and potentialize their anticoagulant effect.

The half-life for eliminating fenofibric acid from plasma is about twenty hours.

Under these conditions, it will be understood that there is no need to take it more than once a day.

It has been observed that fenofibrate has poor solubility in aqueous liquids, thereby giving rise to non-uniform absorption in the digestive tube, and in accordance with the present invention a galenical preparation has been devised which considerably improves absorption by the digestive tube.

SUMMARY OF THE INVENTION

The present invention provides a medicine based on fenofibrate and in the form of granules, each granule comprising an inert core, a layer based on fenofibrate, and a protective layer. In the layer based on fenofibrate, the fenofibrate is present in the form of crystalline microparticles of dimensions not greater than 30 microns, and preferably less than 10 microns.

In accordance with the present invention, this structure is obtained by a method including a step of projecting a damp and sticky outer layer onto the inert cores, followed by a step of projecting fenofibrate microparticles onto the damp layer with the dampness being rapidly evaporated in order to prevent it from dissolving the fenofibrate microparticles while never-the-less fixing said fenofibrate microparticles onto the cores, with said two steps being repeated until a sufficient quantity of fenofibrate has been fixed onto the cores.

The damp and sticky layer may advantageously be constituted by a solution of a polymer in alcohol or by an aqueous suspension of the polymer, and the alcohol solution may be prepared using alcohols which are commonly used in pharmacology.

MORE DETAILED DESCRIPTION

There follows a description, by way of example, of the manufacture of one embodiment of a medicine in accordance with the present invention.

Inert grains for forming the inert cores are prepared in conventional manner. For example, each grain may be a sucrose crystal having a diameter of 0.3 mm. A suspension of maize starch is sprayed onto the crystals, the suspension comprising 27% by weight of maize starch in a hot sugar solution (prepared, for example, by dissolving 73 kg of sugar in 32 kg of water: 27 kg starch, 73 kg sugar, 32 kg water). The sugar solution is projected at 50° C. into a turbine which is itself heated to 50° C. The quantity projected is adjusted so that the diameter of each grain increases from 0.3 mm to 0.6 mm, with the grain having about 25% by weight starch and about 75% sucrose, once the water has evaporated from the sugar solution.

Thereafter, the inert cores are rotated in a turbine and they are dampened with an alcohol solution containing 12.5% by weight of a methylacrylic polymer (95° alcohol). The grains become damp and sticky. Fenofibrate powder is then projected onto them, with the powder being obtained by crushing fenofibrate crystals until microparticles are obtained. A typical powder has the following partical size distribution:

100% < 30 microns
99.5% < 20 microns
98% < 10 microns
88% < 5 microns.

The grains are then immediately dried very rapidly in order to prevent the alcohol from having enough time to dissolve the fenofibrate (a flow of air is passed through the turbine). This avoids destroying the microparticulate structure which offers a considerable

area for encouraging absorption. A single thickness of microparticles is thus deposited on the sticky grain where the microcapsules are fixed by adherence. The operations of dampening-projecting-drying may be performed in about one or two minutes. These operations of dampening the core and projecting microparticles are repeated until all of the powder has been incorporated.

Finally, a protective coating is applied, e.g. a thin layer of methacrylic polymer, representing about 1% by weight of each granule.

Granules obtained in this way are put into capsules, with a dose of 250 mg of fenofibrate per capsule.

The fenofibrate layer structure is similar to that of a sponge, with the pores containing microparticles of fenofibrate. The sponge is constituted by a binder which is soluble in an aqueous medium: methacrylate or polyvinylpyrolidone. Once the binder has dissolved, the microparticles of fenofibrate are released and can prevent their entire areas to the process of absorption in the intestinal aqueous medium.

One example of formulation is as follows:

fenofibrate	400 kg
inert grains	110 kg (sugar and/or starch)
polyvinylpyrolidone and/or methacrylate	20 kg

Of the last 20 kg, about 5 kg are used for making the protective envelope (about 1% of the total weight) and the remainder (about 15 kg) is used for binding the microparticles of fenofibrate, with alcohol being used temporarily as the solvent.

The quantity of binder is determined so that at least 65% of the fenofibrate is released in one hour in a water based liquid medium.

This fraction can be measured as follows: the contents of a capsule is placed in a flask containing 35 ml of a medium having a pH of 1.5. The flask is stirred at 30 rpm and at 37° C. After stirring for one hour, the percentage of fenofibrate that has been released from the galenical preparation in accordance with the invention is greater than 65%.

Composition of the medium:

118 ml normal hydrochloric acid

84 ml solution of normal sodium hydroxide distilled water: enough to obtain 1000.0 ml of medium.

The pH of the medium lies between 1.45 and 1.55.

Medicines in accordance with the invention have also shown reductions in variability of blood concentrations both inter and intra patient (i.e. on the same patient or between different patients).

I claim:

1. Medicine in the form of granules with controlled release of fenofibrate, each granule comprising an inert core, a layer based on fenofibrate and a protective layer, wherein the improvement comprises the layer based on fenofibrate containing the fenofibrate in the form of crystalline microparticles of dimensions not greater than 30 microns, said microparticles being included in the pores of an inert matrix soluble in water.

2. A medicine according to claim 1, wherein the inert matrix is composed by a binder selected from the group comprising: methacrylic polymers, polyvinylpyrolidone, mixtures thereof; cellulose derivatives; and polyethylene glycols.

3. A medicine according to claim 1, wherein the inert core has a diameter of about 0.3 mm to about 0.6 mm and is constituted by a substance selected from the group comprising: glucose, sucrose, lactose, and their equivalents, and starch, and mixtures thereof.

4. A medicine according to claim 1, wherein the protective layer represents about 1% by weight of each granule, and is formed of a substance selected from the group comprising: methacrylic polymers, polyvinylpyrolidone, mixtures thereof; cellulose derivatives; and polyethylene glycols.

5. A medicine according to claim 1, wherein the quantity of binder is such that the quantity of fenofibrate liberated in one hour in an aqueous liquid is not less than 65%.

6. Medicine according to claim 1 wherein the dimensions of said microparticles are less than 10 microns.

7. Medicine according to claim 3 wherein the starch is maize starch.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 4,800,079

DATED : January 24, 1989

INVENTOR(S) : Jean-Francois Boyer

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Title page, the following should be inserted:

--[73] Assignee: ETHYPHARM
Houdan, France--

Signed and Sealed this

Nineteenth Day of December, 1989

Attest:

JEFFREY M. SAMUELS

Attesting Officer *Acting Commissioner of Patents and Trademarks*

EXHIBIT 4

US006074670A

United States Patent [19]

Stamm et al.

[11] Patent Number: 6,074,670

[45] Date of Patent: Jun. 13, 2000

[54] **FENOFIBRATE PHARMACEUTICAL COMPOSITION HAVING HIGH BIOAVAILABILITY AND METHOD FOR PREPARING IT**

[75] Inventors: **André Stamm**, Griesheim, France; **Pawan Seth**, Irvine, Calif.

[73] Assignee: **Laboratoires Fournier, S.A.**, Dijon, France

[21] Appl. No.: **09/005,128**

[22] Filed: **Jan. 9, 1998**

[30] **Foreign Application Priority Data**

Jan. 17, 1997 [FR] France 97 00479

[51] **Int. Cl.**[7] **A61K 9/16**; A61K 9/20; A61K 9/50

[52] **U.S. Cl.** **424/462**; 424/456; 424/458; 424/459; 424/489; 424/490; 424/497; 424/464; 424/465; 424/469; 424/470

[58] **Field of Search** 424/465, 464, 424/470, 472, 479, 482, 489, 2.15, 451, 456, 458, 462, 490, 497

[56] **References Cited**

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4,412,986	11/1983	Kawata et al. .
4,800,079	1/1989	Boyer .
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5,776,495	7/1998	Duclos et al. .

FOREIGN PATENT DOCUMENTS

256 933	2/1988	European Pat. Off. .
330 532	8/1989	European Pat. Off. .
519 144	12/1992	European Pat. Off. .
92/01649	5/1982	WIPO .
98/31361	7/1998	WIPO .

OTHER PUBLICATIONS

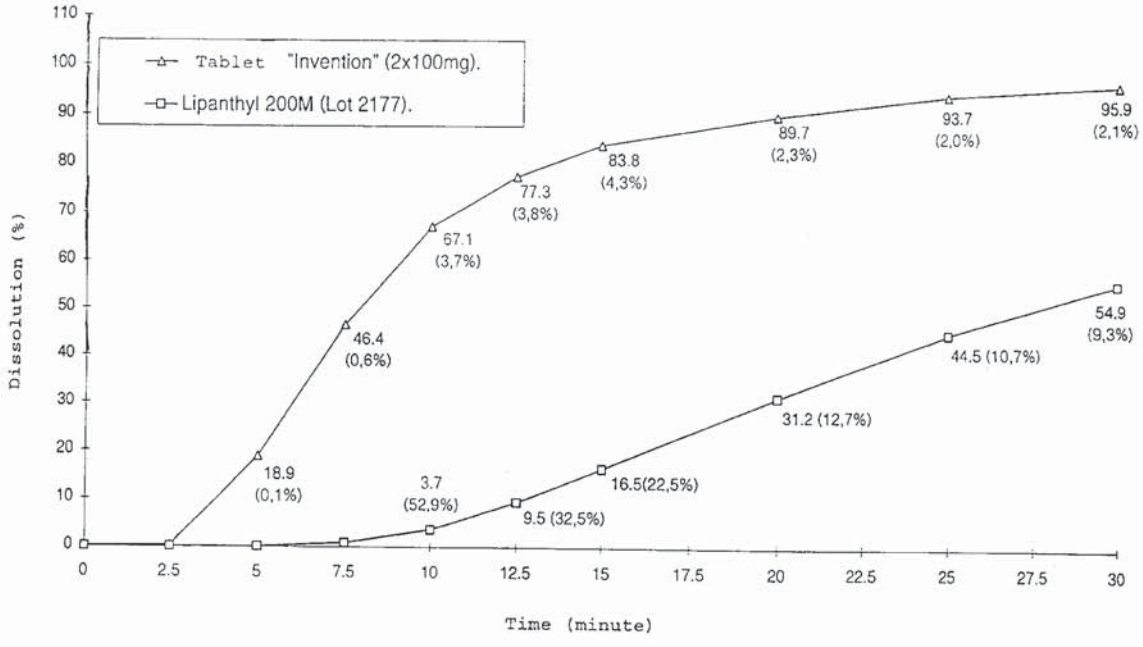
Temeljotov et al., Solubilization and Dissolution Enhancement for Sparingly Soluble Fenofibrate, Acta Pharm., 46 pp 131–136, 1996.

Primary Examiner—Thurman K. Page
Assistant Examiner—Brian K. Seidleck
Attorney, Agent, or Firm—Hale and Dorr LLP

[57] **ABSTRACT**

The invention provides an immediate-release fenofibrate composition comprising (a) an inert hydrosoluble carrier covered with at least one layer containing fenofibrate in a micronized form having a size less than 20 μm, a hydrophilic polymer and, optionally, a surfactant, the polymer making up at least 20% by weight of (a); and (b) optionally one or several outer phase(s) or layers(s). The invention also provides a method for preparing said composition.

38 Claims, 2 Drawing Sheets



FENOFIBRATE PHARMACEUTICAL COMPOSITION HAVING HIGH BIOAVAILABILITY AND METHOD FOR PREPARING IT

BACKGROUND OF THE INVENTION

The present invention relates to a novel pharmaceutical composition having high bioavailability through improved dissolution, and a method for preparing it. The invention more particularly relates to a pharmaceutical composition for administration by oral route, containing an active ingredient of poor aqueous solubility.

Numerous active ingredients suffer from the disadvantage of being poorly soluble in an aqueous medium, thus having an insufficient dissolution profile and, consequently, poor bioavailability within the organism, following oral administration. The therapeutic dose required to be administered must thus be increased in order to obviate this disadvantage. This particularly applies to numerous hypolipemiant active ingredients, such as those belonging to the fibrate family.

Fenofibrate is a well-known hypolipemiant from the family of fibrates, which is commercially available in various doses (100 and 300 mg for example Secalip®) but in a form leading to poor bioavailability of the active ingredient. Indeed, due to it poor hydrosolubility, fenofibrate is poorly absorbed in the digestive tract and consequently its bioavailability is incomplete, irregular and often varies from one person to another.

To improve the dissolution profile of fenofibrate and its bioavailability, thereby reducing the dose requiring to be administered, it would be useful to increase its dissolution so that it could attain a level close to 100%.

Moreover, for patient comfort, it is advantageous to seek a dosage form that only requires the medicament to be taken once daily while giving the same effect as one administered several times daily.

EP-A-0330532 discloses a method for improving bioavailability of fenofibrate. This patent describes the effect of co-micronizing fenofibrate with a surfactant, for example sodium laurylsulfate in order to improve fenofibrate solubility and thereby increase its bioavailability. This patent teaches that co-micronizing fenofibrate with a solid surfactant improves fenofibrate bioavailability to a much greater extent than the improvement that would be obtained either by adding a surfactant, or through solely micronizing the fenofibrate, or, yet again, through intimately mixing the fenofibrate and surfactant, micronized separately. The dissolution method employed is the conventional rotating blade technique (European Pharmacopoeia): product dissolution kinetics are measured in a fixed volume of the dissolution medium, agitated by means of a standardized device; a test was also carried out with an alternative technique to the European Pharmacopoeia, using the continuous-flow cell method.

The process of EP-A-0330532 leads to a new dosage form in which the active ingredient, co-micronized with a solid surfactant, has improved fenofibrate dissolution, and thus increased bioavailability, which makes it possible, for a given level of effectiveness, to decrease the daily dose of the medicament: respective 67 mg and 200 mg instead of 100 mg and 300 mg.

However, the preparation method in that patent is not completely satisfactory inasmuch as it does not lead to complete bioavailability of the active ingredient, and suffers from several disadvantages. The technique of co-micronizing fenofibrate with a solid surfactant does, it is true, improve dissolution of the active ingredient, but this dissolution remains, however, incomplete.

There is thus a need to improve fenofibrate bioavailability in order to attain, over very short periods of time, a level close to 100% (or, in any case, better than the following limits: 10% in 5 minutes, 20% in 10 minutes, 50% in 20 minutes and 75% in 30 minutes in a medium consisting of 1200 ml water to which 2% Polysorbate 80 is added, or of 1000 ml of water to which 0.025M sodium lauryl sulfate sodium is added, with a blade rotation speed of 75 rpm), and this even when dissolution media having a low surfactant content are used.

Applicant has found that, surprisingly, it is possible to resolve this problem by a new method for preparing a pharmaceutical composition by spraying a suspension of the active ingredient onto an inert hydrosoluble carrier. The present invention also relates to pharmaceutical compositions thus prepared.

The use is already known of a polymer, such as polyvinylpyrrolidone for producing tablets, in concentrations of the order of 0.5 to 5% by weight, at a maximum 10% by weight. In this case, the polyvinylpyrrolidone is used as a binder. Similarly, the use of a polymer such as hydroxymethylpropylmethyl cellulose as a granulation binder is known. Thus, European patent application 0,519,144 discloses pellets of a poorly soluble substance, omeprazole, obtained by spraying a dispersion or suspension of the active ingredient in a solution containing said polymer onto inert pellets in a fluidized-bed granulator. However, here again, the polymer (HPMC and HPC) is only used as a granulation binder, in an amount of about 50% by weight, based on the weight of the active ingredient, which, bearing in mind the presence of the inert pellets of a large size (about 700 μm) and the overall final weight leads to final active ingredient and polymer contents which are very low, of the order of barely a few percent based on the weight of the final covered pellet. Finally, it will be noted that the size of the inert pellets in this documents is fairly large, which, in the case of fenofibrate, would lead to a final formulation having a volume which is much too large for ready oral administration.

The use of polymer, such as polyvinylpyrrolidone for manufacturing "solid dispersions" is also known, obtained in general by co-precipitation, co-fusion or liquid-phase mixing followed by drying. What we have here is fixation of the active ingredient in isolated microparticles on the polyvinylpyrrolidone, which avoids problems of poor wetting of the solid and re-agglomeration of the particles. The article "Stable Solid Dispersion System Against Humidity" by Kuchiki et al., Yakuzaigaku, 44 No. 1, 31–37 (1984) describes such a technique for preparing solid dispersions using polyvinylpyrrolidone. The amounts of PVP here are very high, and the ratio between the active ingredient and PVP are comprised between 1/1 and 1/20. In the case however there is no inert carrier.

WO-A-96 01621 further discloses a sustained release composition, comprising an inert core (silica in all examples) coated with a layer which contains the active ingredient in admixture with a hydrophilic polymer, the weight ratio active ingredient/polymer being comprised between 10/1 and 1/2 and the weight ratio active ingredient/inert core being comprised between 5/1 and 1/2, with an outer layer to impart the sustained release property. These compositions can be compressed. The hydrophilic polymer can be polyvinylpyrrolidone. This document also discloses a

EXHIBIT 5

PCT

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(30) Priority Data:
08/672,432 28 June 1996 (28.06.96) US

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(74) Agents: MAJKA, Joseph, T. et al.; Schering-Plough Corporation, Patent Dept. K-6-1 1990, 2000 Galloping Hill Road, Kenilworth, NJ 07033-0530 (US).

(81) Designated States: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CZ, EE, GE, HU, IL, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: ORAL COMPOSITION COMPRISING A TRIAZOLE ANTIFUNGAL COMPOUND

(57) Abstract

A pharmaceutical composition comprising: i) substantially inert beads; wherein said beads are coated with ii) an antifungal agent which is (-)-(2R-cis)-4-[4-[4-[4-[[-5-(2,4-difluorophenyl)-tetrahydro-5-(1H-1,2,4-triazol-1-ylmethyl)furan-3-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-[(S)-1-ethyl-2(S)-hydroxypropyl]-3H-1,2,4-triazol-3-one; iii) a binder to enable the antifungal compound to adhere to said beads. The composition enables the antifungal compound, which has very low water solubility, to have enhanced bioavailability in mammals, such as humans.

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ORAL COMPOSITION COMPRISING A TRIAZOLE ANTIFUNGAL COMPOUND

BACKGROUND OF THE INVENTION

The present invention relates to compositions having enhanced or improved bioavailability for a novel triazole antifungal compound.

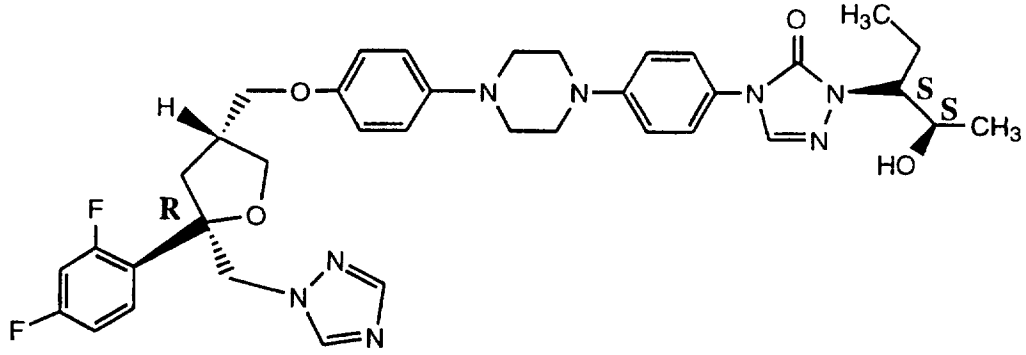
International Patent Publication Number WO 95/17407 published 29 June 1995, teaches a novel class of tetrahydrofuran/triazole antifungal compounds. One particular compound, (2R-cis)-4-[4-[4-[4-[[-5-(2,4-difluorophenyl)-tetrahydro-5-(1H-1,2,4-triazol-1-ylmethyl)furan-3-yl]methoxy]phenyl]-1-piperazinyl]phenyl]2-4-dihydro-2-[(S)-1-ethyl-2(S)-hydroxypropyl]-3H-1,2,4-Triazol-3-One ("the antifungal compound"), was found to have potent antifungal activity in suspensions against opportunistic fungi such as Aspergillis, Candida, Cryptococcus and other opportunistic fungi. However, solid compositions, such as powders or granules, were found to have reduced anti-fungal activity and/or bioavailability, presumably due to this compound's extremely low water solubility. It would be desirable to provide this antifungal compound in a pharmaceutical composition whose antifungal and/or bioavailabilty would be enhanced or improved.

SUMMARY OF THE INVENTION

The present invention is directed to a pharmaceutical composition comprising:

i) a plurality of beads; wherein said beads are coated with

ii) an antifungal agent of the formula:



; and

iii) a binder to enables the antifungal compound to adhere to said beads.

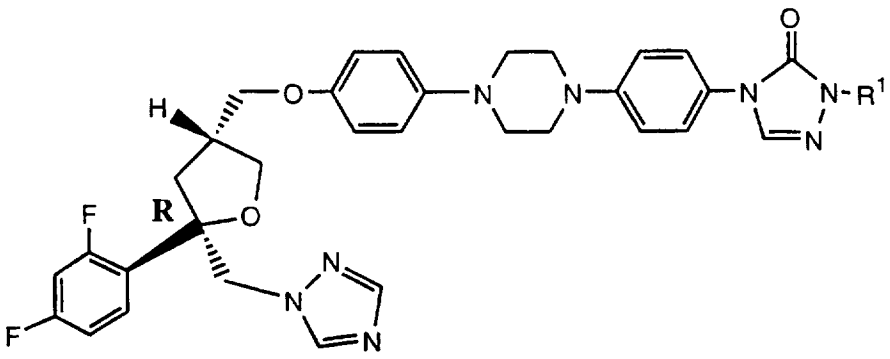
The pharmaceutical composition may also contain other excipients such as iv) surfactants, v) plasticizers, vi) defoaming agents and coloring agents. The pharmaceutical composition can also be formulated into any other suitable delivery system or dosage form, such as capsules, tablets, or beads for reconstitution.

It has also been surprisingly and unexpectedly found that the coating of beads with the antifungal compound using a suitable binder, can enhance or be equivalent to the bioavailability of the antifungal compound compared to suspensions. These results are truly surprising and unexpected, since known references, such as Peter G. Welling, Pharmacokinetics, Processes and Mathematics, American Chemical Society, Washington DC, ACS Monograph 185, 1986, page 57, teaches that solutions and suspensions generally give rise to more satisfactory bioavailability than capsules or tablets. J.G. Nairn, Remington's Pharmaceutical Sciences, 18th Edition, 1990, Mack Publishing Co., Chapter 83, page 1519 also teaches that since drugs are absorbed in their dissolved state, frequently it is found that the absorption rate of oral dosage forms decreases in the following order: aqueous solution>aqueous suspension>capsule or tablet.

The present invention has the advantage of being able to provide the antifungal compound in a pharmaceutical composition that can conveniently be formulated into solid or "dry" delivery systems or dosage forms such as capsules, tablets or loose beads having effective antifungal activity and/or bioavailabilty.

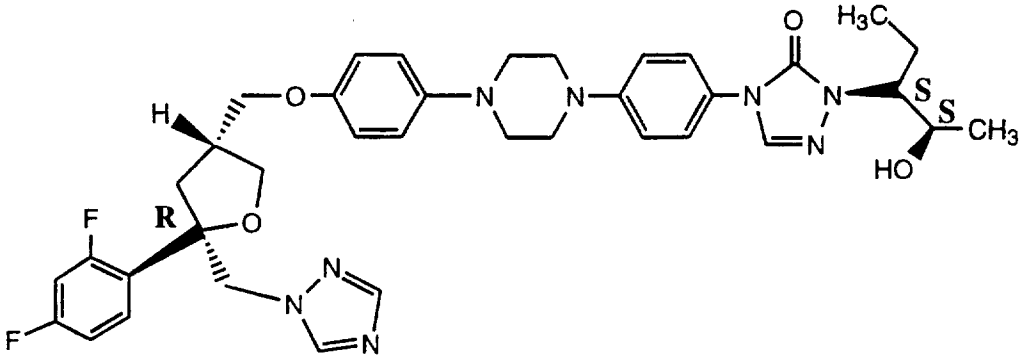
DETAILED DESCRIPTION OF THE EMBODIMENTS

WO 95/17407 published 29 June 1995 discloses antifungal compounds of the formula:



wherein R^1 is a straight or branch chain (C3 to C8) alkyl group substituted by one or two hydroxy moieties; esters and ethers thereof or a pharmaceutically

acceptable salt thereof. An especially preferred compound of the above group taught in Examples 24 and 32 of WO 95/17407 is the antifungal compound, (-)-(2R-cis)-4-[4-[4-[4-[[-5-(2,4-difluorophenyl)-tetrahydro-5-(1H-1,2,4-triazol-1-ylmethyl)furan-3-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,-4-dihydro-2-[(S)-1-ethyl-2(S)-hydroxypropyl]-3H-1,2,4-triazol-3-one ("the antifungal compound"); Formula: $C_{37}H_{42}F_2N_8O_4$; Molecular weight: 700.8; m.p. 164-165°C, $[a]_D^{25}$ -29°C ± 3° (c = 1.0, $CHCl_3$), whose structure is depicted below:



Micron-sized particles of the antifungal compound can be obtained either by the final step during the manufacture of the antifungal compound or by the use of conventional micronizing techniques after the conventional crystallization procedure(s).

Where micronizing techniques are employed, the antifungal compound may be micronized to the desired particle size range by conventional techniques, for example, using a ball mill, ultrasonic means, or preferably using fluid energy attrition mills such as the trost fluid energy mill from Plastomer Products, Newton, Pennsylvania 18940. When using a fluid energy attrition mill, the desired particle size can be obtained by varying the feed rate of the antifungal into the mill.

About 99% of the of the micronized antifungal particle are less than or equal to 100 microns in length, of which 95% are less than or equal to 90 microns. Preferably, about 99% of the micronized particles are less than or equal to 50 microns, of which 95% are less than or equal to 40 microns. More preferably, 99% of the micronized particles are less than or equal to 20 microns, of which 95% are less than or equal to 10 microns.

The antifungal compound is employed in the composition in amounts effective to control the organism or fungi of interest. Such amounts can range from about 2% to about 50% by weight of the composition, more preferably from 6% to about 40%, most preferably from about 5 to about 33% by weight. The

amount of composition in the particular dosage form, e.g. capsule, tablet, etc., can range from about 10 to about 300 mg antifungal compound per dosage form, preferably from about 50 to about 200 mg.

Compositions of the present invention can be prepared by dissolving or suspending the antifungal compound in an a suitable solvent system containing a binder, and optionally with one or more ingredients such as a surfactant, plasticizer, defoaming agent and/or coloring agent and coating the solution or suspension on the inert beads.

The pharmaceutical composition of the present invention can be formulated into any suitable dosage form, such as capsules, tablets or loose beads for constitution. For example, the above composition can be compressed into tablet form using a suitable cushioning agent, such as microcrystalline cellulose, and optionally, a disintegrant, lubricant, glident, and the like.

The following terms are used to describe the present pharmaceutical compositions, ingredients which can be employed in its formulation and methods for assessing its bioactivity or bioavailability.

The beads or seeds are discrete particles, preferably spherical particles or spheres, which serve as the solid substrate upon which the antifungal compound is coated, and make up the major portion of the composition or dosage form. Beads can be made of sugars such as lactose, sucrose, mannitol and sorbitol; other beads can be derived from starches derived from wheat, corn rice and potato; and celluloses such as microcrystalline cellulose. A source of sugar beads (non-pareil seeds) is known as Nu-pareil PG, tradename of Crompton and Knowles Ingredient Technology Corporation, of Mahawah, New Jersey. A source of microcrystalline cellulose beads is known as Celphere, tradename of the FMC Corporation, Philadelphia, Pennsylvania. Beads of differing mesh sizes can be employed, such as 18/20 mesh, 25/30 mesh and 40/50 mesh. Such mesh sizes refer to particle or bead sizes whose diameters can ranges from about 1.0 millimeters (mm) to about 0.297 mm. Preferably the bead sizes or diameters are within a relative narrow range such as, for example, between about 1.0-0.84 mm (18/20 mesh), or between about 0.71-0.59 mm (25/30 mesh), or between about 0.42-0.297 mm (40/50 mesh). The beads should be "inert" meaning that the beads themselves have little or no antifungal effectiveness. The amount of beads in the composition can range

from about 50 to about 90% by weight of the total composition, preferably from about 60 to about 80%, more preferably from about 65 to about 75% by weight.

Binders - refers to substances that bind or "glue" the antifungal compound and other ingredients onto the beads, enabling the beads to be coated. Suitable binders include sugars such as sucrose; starches derived from wheat, corn rice and potato; natural gums such as acacia, gelatin and tragacanth; derivatives of seaweed such as alginic acid, sodium alginate and ammonium calcium alginate; cellulosic materials such as methylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, hydroxyethylcellulose and sodium carboxymethylcellulose; polyvinylpyrrolidone (Povidones); protein hydrolysates; methacrylic acid and salts thereof; and inorganic compounds such as magnesium aluminum silicate. A commercially available formulation useful as a binder is known as Opadry powders, tradename of the Coloron Corporation, West Point, Pennsylvania. Opadry powders may contain hydroxypropylmethylcellulose, along with a plasticizer such as polyethylene glycol and a surfactant such as polysorbate-80. The amount of binder in the composition can range from about 1 to about 10% by weight of the composition, preferably from about 2 to about 8% by weight, more preferably from about 3 to about 6%.

Disintegrants - refers to materials added to the composition to help it break apart (disintegrate) and release the medicaments. Suitable disintegrants include starches; "cold water soluble" modified starches such as sodium carboxymethyl starch; natural and synthetic gums such as locust bean, karaya, guar, tragacanth and agar; cellulose derivatives such as methylcellulose and sodium carboxymethylcellulose; microcrystalline celluloses and cross-linked microcrystalline celluloses such as sodium croscarmellose; alginates such as alginic acid and sodium alginate; clays such as bentonites; and effervescent mixtures. The amount of disintegrant in the composition can range from about 2 to about 15% by weight of the composition, more preferably from about 4 to about 10% by weight.

Surfactant - refers to a compound that can reduce the interfacial tension between two immiscible phases and this is due to the molecule containing two localized regions, one being hydrophilic in nature and the other hydrophobic.

Non-ionic surfactant - refers to a surfactant which lacks a net ionic charge and do not dissociate to an appreciable extent in aqueous media. The

properties of non-ionic surfactants are largely dependent upon the proportions of the hydrophilic and hydrophobic groups in the molecule. Hydrophilic groups include the oxyethylene group (-OCH_2CH_2-) and the hydroxy group. By varying the number of these groups in a hydrophobic molecule, such as a fatty acid, substances are obtained which range from strongly hydrophobic and water insoluble compounds, such as glyceryl monostearate, to strongly hydrophilic and water-soluble compounds, such as the macrogols. Between these two extremes types include those in which the proportions of the hydrophilic and hydrophobic groups are more evenly balanced, such as the macrogol esters and ethers and sorbitan derivatives. Suitable non-ionic surfactants may be found in Martindale, The Extra Pharmacopoeia, 28th Edition, 1982, The Pharmaceutical Press, London, Great Britain, pp. 370 to 379. Such non-ionic surfactants include block copolymers of ethylene oxide and propylene oxide, glycol and glyceryl esters of fatty acids and their derivatives, polyoxyethylene esters of fatty acids (macrogol esters), polyoxyethylene ethers of fatty acids and their derivatives (macrogol ethers), polyvinyl alcohols, and sorbitan esters. Preferably, the non-ionic surfactant is a block copolymer of ethylene oxide and propylene oxide.

Suitable block copolymers of ethylene oxide and propylene oxide generically called "Poloxamers" and include those represented by the following chemical structure:

$$HO(CH_2CH_2O)_a(\underset{\displaystyle CH_3}{\underset{|}{CH_2CHO}})_b(CH_2CH_2O)_aH$$

wherein a is an integer ranging from about 10 to about 110, preferably from about 12 to 101; more preferably from about 12 to 80; and

b is an integer ranging from about 20 to about 60, more preferably from about 20 to about 56; also from about 20 to 27. Most preferably, a is 80 and b is 27, otherwise known as Pluronic®F68 surfactant, trademark of the BASF Corporation, Mount Olive, New Jersey, USA. Pluronic®F68 surfactant is also known as Poloxamer 188. This surfactant has an average molecular weight of 8400, is a solid at 20°C, has a viscosity (Brookfield) of 1000 cps at 77°C. Other suitable block copolymers of ethylene oxide and propylene oxide include Pluronic F87, also known as Poloxamer 237 wherein a is 64 and b is 37; and Pluronic F127, also known as Poloxamer 407 wherein a is 101 and b is 56.

Suitable glycol and glyceryl esters of fatty acids and their derivatives include glyceryl monooleate and similar water soluble derivatives;

Suitable polyoxyethylene esters of fatty acids (macrogol esters) include polyoxyethylene castor oil and hydrogenated castor oil derivatives;

Suitable polyoxyethylene ethers of fatty acids and their derivatives (macrogol ethers) include Cetomacrogel 1000, Lauromacrogols (a series of lauryl ethers of macrogols of differing chain lengths) e.g. Laureth 4, Laureth 9 and Lauromacrogol 400.

Suitable Sorbitan esters (esters of one or more of the hydroxyl groups in the sorbitans, with a fatty acid, such as stearic, palmitic, oleic or lauric acid) include, e.g. Polysorbate 20, Polysorbate 40, Polysorbate 60, Polysorbate 65, Polysorbate 80, Polysorbate 85, Sorbitan Monolaurate, Sorbitan Mono-oleate, Sorbitan Monopalmitate, Sorbitan Monostearate, Sorbitan Sesquioleate, Sorbitan Trioleate and Sorbitan Tristearate.

The amount of surfactant in the composition can range from about 0.5 to about 25% by weight of the total composition, more preferably from about 5 to about 15% by weight.

Anionic surfactant - refers to a surfactant which has a net negative ionic charge and dissociates to an appreciable extent in aqueous media. Optionally, the present composition may also contain an anionic surfactant, e.g. sodium lauryl sulfate, the amount of which can range from about 1 to about 10% by weight of the total composition, more preferably from about 3 to about 8% by weight.

Plasticizers-refers to substances which make the binder flexible. Suitable plasticizers include propylene glycol, glycerin, diethylphthalate, dibutyl sebacate, triethyl citrate, hydrogenated glycerides, polyethylene glycols, polyethylene oxides, triacetin and the like. The amount of plasticizer in the composition can be in the range of about 1-2 to about 5% by weight.

Defoaming agents, also known as antifoaming agents, are substances used to reduce foaming due to mechanical agitation or to gases, nitrogenous materials or other substances which may interfere during processing. Examples include metallic salts such as sodium chloride; C6 to C12 alcohols such as octanol; sulfonated oils; silicone ethers such as simethicone; organic phosphates and the like. The amount of defoaming agent in the composition can range from about 0.05 to 5%, preferably from about 0.1 to 2%.

Glidents - materials that prevent caking and improve the flow characteristics of granulations, so that flow is smooth and unifom. Suitable

glidents include silicon dioxide and talc. The amount of glident in the composition can range from about 0.1% to about 5% by weight of the total composition, preferably from about 0.5 to about 2% by weight.

Lubricant - refers to a substance added to the dosage form to enable the tablet, granules, etc. after it has been compressed, to release from the mold or die by reducing friction or wear. Suitable lubricants include metallic stearates such as magnesium, calcium or potassium stearate; stearic acid; high melting point waxes; and water soluble lubricants such as sodium chloride, sodium benzoate, sodium acetate, sodium oleate, polyethylene glycols and d'l-leucine. Lubricants are usually added at the very last step before compression, since they must be present on the surfaces of the granules and in between them and the parts of the tablet press. The amount of lubricant in the composition can range from about 0.2 to about 5% by weight of the composition, preferably from about 0.5 to about 2%.

Coloring agents - excipients that provide coloration to the composition or the dosage form. Such excipients can include food grade dyes and food grade dyes adsorbed onto a suitable adsorbent such as clay or aluminum oxide. The amount of the coloring agent can vary from about 0.1 to about 5% by weight of the composition, preferably from about 0.1 to about 1%.

Dosage form - composition containing the antifungal compound formulated into a delivery system, i.e., tablet, capsule, oral gel, powder for constitution or suspension in association with inactive ingredients.

Capsule - refers to a special container or enclosure made of methyl cellulose, polyvinyl alcohols, or denatured gelatins or starch for holding or containing compositions comprising the active antifungal compound. Hard shell capsules are typically made of blends of relatively high gel strength bone and pork skin gelatins. The capsule itself may contain small amounts of dyes, opaquing agents, plasticizers and preservatives.

Tablet- refers to a compressed or molded solid dosage form containing the active ingredient (antifungal compound) with suitable diluents. The tablet can be prepared by compression of mixtures or granulations obtained by wet granulation, dry granulation, compaction or compression of mixtures containing coated active beads.

Beads for constitution refers to the loose, coated beads which can be suspended in water, juices or sauces such as applesauce.

Bioavailability - refers to the rate and extent to which the active drug ingredient or theraputic moiety is absorbed into the systemic circulation from an administered dosage form as compared to a standard or control.

C_{max} values refers to the maximum concentration of the antifungal compound measured (i.e. "peak") in the plasma serum.

AUC (0-72 hr) values refer to the area under the plasma/serum concentration-time curve for the antifungal over a designated time.

Conventional methods for preparing tablets are known. Such methods include dry methods such as direct compression and compression of granulation produced by compaction, or wet methods or other special procedures.

The following examples describe compositions of the present invention containing the antifungal compound, but they are not to be interpreted as limiting the scope of the claims.

Example 1. Coated Beads in Capsules

Ingredient	g/batch	% wt basis
Antifungal compound, micronized	135	20.3
Opadry YS-1-7006	30	4.5
Simethicone	1.42	0.2
Water purified, USP (evaporates)	700 mL	-
Non-Pareil Seeds (25/30 mesh)	500	75
	666.42	100%

Example 2. Coated Beads in Capsules

Ingredient	mg/batch	% wt basis
Antifungal compound, micronized	75	11.0
Opadry YS-1-7006	30	4.4
Pluronic F68 surfactant	75	11.0
Simethicone	0.7	0.1
Water purified, USP (evaporates)	500 mL	-
Non-Pareil Seeds (25/30 mesh)	500	73.5
	680.7	100%

Preparation of Coated Beads in Capsules in Examples 1, 2 and 5

Dissolve the Opadry YS-1-7006, Pluronic F68 or sodium lauryl sulfate in water. Add simethicone while stirring. Add the antifungal compound while stirring slowly until a homogeneous suspension is formed. Screen the suspension through a 25 mesh hand screen. Spray the suspension onto the non-pareil seeds using a fluid bed coater. Dry the coated beads overnight and assay the coated beads to determine the amount of antifungal compound. Fill the coated beads into suitable size capsules to the requisite fill weight.

Preparation of Aqueous Suspension in Comparative Example 3

Prepare a suspension containing 59.8 mg Pluronic F68 in four mL of distilled water. Add 200 mg of antifungal compound to the above solution and mix to give a homogeneous suspension.

Preparation of Powder Mixture in Capsules in Comparative Example 4

Ingredient	mg/capsule	% wt basis
Antifungal compound, micronized	100.0	28.6
Sodium lauryl sulfate surfactant	22.5	6.4
Microcrystalline cellulose	178.0	50.9
Sodium starch glycolate	45.0	12.8
Magnesium stearate	4.5	1.3
	350	100

Mix the antifungal compound, sodium lauryl sulfate (a surfactant), microcrystalline cellulose, and sodium starch glycolate in a blender for 10 minutes. Add magnesium stearate and mix for 5 minutes to form a homogeneous powder. Fill the powder into suitable size capsules to the requisite fill weight.

Testing for Bioavailability

Dogs are administered a 200 mg dose of the antifungal compound using two capsules or in suspension. Samples of serum are collected at selected times and analyzed by an HPLC/UV detection procedure using a high pressure liquid chromatograph equipped with an ultra-violet detector. In the table below, the C_{max} and AUC (0-72 hr) values are indicators of the antifungal compound's bioavailability. The larger the AUC value, the greater the total amount of antifungal compound that accumulated in the plasma serum over the 72 hour period.

Indicator of Bioavailabillity	Coated Beads in Capsules- Example 1	Coated Beads in Capsules- Example 2	Control Suspension- Comparative Example 3	Powder Mixture in Capsules- Comparative Example 4
C_{max} (ug/ml)	1.43	1.37	1.21	0.95
$AUC_{(0\text{-}72\ hr)}$ ug/hr/ml	50.21	50.17	47.98	29.72

The results above show that capsules of Examples 1 and 2 exhibit enhanced bioavailability over that of the aqueous suspension of Comparative Example 3 and especially over the powdered mixture in capsules of Comparative Example 4.

Example 5. Coated Beads in Capsules

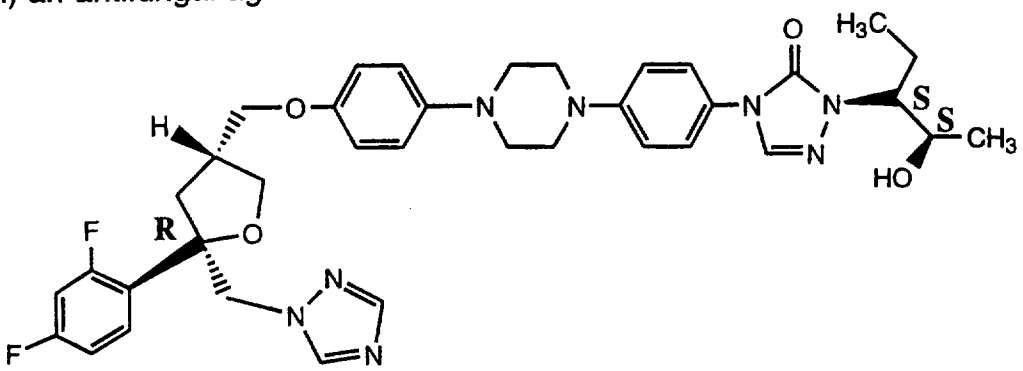
Ingredient	g/batch	% wt basis
Antifungal compound, micronized	75.0	11.80
Opadry YS-1-7006	30.0	4.72
Sodium lauryl sulfate	30.0	4.72
Simethicone	1.0	0.16
Water purified, USP (evaporates)	500 mL	-
Non-Pareil Seeds (25/30 mesh)	500.0	78.60
	636.0	100%

WHAT IS CLAIMED IS:

1. A pharmaceutical composition comprising:

i) a plurality of beads; wherein said beads are coated with

ii) an antifungal agent of the formula:



; and

iii) a binder to enables the antifungal compound to adhere to said beads.

2. The composition of claim 1 wherein the beads are made of sugar, starch or microcrystalline cellulose.

3. The composition of claim 1 wherein the beads are made of sugar.

4. The composition of claim 1 wherein the beads have a mesh size ranging between about 18/20 to 45/50.

5. The composition of claim 1 wherein the amount of antifungal compound in the composition can range from about 5 to about 33% by weight.

6. The composition of claim 1 wherein the binder is hydroxypropylmethylcellulose.

7. The composition of claim 1 further comprising

iv) a surfactant.

8. The composition of claim 7 wherein the surfactant is a non-ionic surfactant.

9. The composition of claim 7 wherein the surfactant is a block copolymer of ethylene oxide and propylene oxide.

10. The composition of claim 7 wherein the surfactant is an anionic surfactant.

11. The composition of claim 10 wherein the anionic surfactant is sodium lauryl sulfate.

12. The composition of claim 7 further comprising
v) a plasticizer.

13. The composition of claim 12 wherein the plasticizer is polyethylene glycol.

14. The composition of claim 13 further comprising
vi) a defoaming agent.

15. The composition of claim 14 wherein the defoaming agent is simethicone.

16. The composition of claim 1 in the dosage form of a capsule.

17. The composition of claim 16 wherein the amount of antifungal compound in the capsule is in the range of about 50 to 300 milligrams.

18. The composition of claim 16 wherein the amount of antifungal compound in the capsule is in the range of about 50 to 200 milligrams.

19. The pharmaceutical composition of claim 1 further comprising
about 11-20% by weight of the antifungal compound;
about 73-75% by weight beads;
about 0.5-15% by weight of a surfactant;
about 4.7-5% by weight of a binder which is hydroxypropylmethyl cellulose; and
about 0.5-1.5% by weight of a defoaming agent.

INTERNATIONAL SEARCH REPORT

Intern onal application No.
PCT/US 97/10122

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 9/50, A61K 9/16, A61K 31/495
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K, A01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAPLUS, WPI, USPATFULL, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9405263 A1 (JANSSEN PHARMACEUTICA N.V.), 17 March 1994 (17.03.94), page 2, line 23 - page 3, line 13; page 3, line 24 - line 35	1-19
A	WO 9517407 A1 (SCHERING CORPORATION), 29 June 1995 (29.06.95)	1-19
A	EP 0636366 A2 (EUROCELTIQUE S.A.), 1 February 1995 (01.02.95)	1-19

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 October 1997	11. 11. 97
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+ 31-70) 340-3016	Authorized officer Anneli Jönsson

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INTERNATIONAL SEARCH REPORT

SA 64718

Information on patent family members

01/10/97

International application No.
PCT/US 97/10122

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